Allergic Bronchopulmonary Aspergillosis – A Clinical Review

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Abstract

Allergic Bronchopulmonary Aspergillosis (ABPA) was first described by Hinson and colleagues in 1952. ABPA is a hypersensitivity disorder induced by a fungus Aspergillus and affects non-immunocompromised patients. The diagnosis is based on the presence of a combination of clinical, biological and radiological criteria. The treatment is based on oral corticosteroids for 6–8 weeks at acute phase or exacerbation and Itraconazole is now recommended and validated at a dose of 200 mg/day for 16 weeks.

Introduction

Aspergillus species are ubiquitous spore-forming fungi present in the environment. There are about 180 species of Aspergillus but the common ones which affect the humans are Aspergillus fumigates (AF), Aspergillus flavus, Aspergillus niger. A variety of clinical manifestations can be caused by these three species ranging from colonization in allergic bronchopulmonary disease to active infection in locally destructive disease, or in the most severe form as disseminated infection in immunocompromised patients. ABPA was first reported by Hinson and his colleagues and a detailed description of the disease was done by Pepys and coworkers. Allergic Bronchopulmonary Aspergillosis (ABPA) is a hypersensitivity reaction to Aspergillus mycelia that colonize the bronchi. Asthma and cystic fibrosis are the common illnesses associated with ABPA. The prevalence of ABPA is reported to be 1-2% in asthmatics, 7-14% in steroid-dependent asthmatics, and 2-15% in cystic fibrosis (CF). Both environmental factors and a genetic predisposition may be present as far as the prevalence of the disease in asthmatics is concerned. The familial occurrence of ABPA supports the same. The HLA-DR molecules, especially DR2, DR5, and possibly DR4 and DR-7, are associated with susceptibility to ABPA, while HLA-DRQ2 has shown to have resistance to ABPA. On the other hand in the patients with cystic fibrosis, the presence of atopy with underlying impaired mucociliary clearance and airway inflammation renders them susceptible toward developing ABPA.

Epidemiology

In India first three cases of ABPA were reported in 1971. Since then a number of cases have been reported from different regions of India including the largest one by Agarwal et al from North India. Following this the condition is being increasingly recognised in the country. Although ABPA is relatively common in adults between 20–40 years of age, many cases have been reported from younger age groups in India. Youngest case of ABPA was reported by Gaur et al and the patient was only four years old. Majority of ABPA cases occur in patients of bronchial asthma and cystic fibrosis. Several attempts have been made to estimate the prevalence of ABPA but the lack of uniform diagnostic criteria and standardized tests make it a tough task. Kumar and Gaur from India reported 16% ABPA prevalence in asthmatics. Mauya et al, in their study of 105 patients with bronchial asthma reported ABPA prevalence of 7.5%. Recently, Agarwal et al reported ABPA prevalence to be 27.2% in their study of 564 asthmatics from North India. But these figures are virtual overestimate of the actual prevalence of the entity due to the selection bias of the subjects to the tertiary level institutes.

ABPA is still under recognized and under diagnosed in our country, inspite of its relatively high prevalence. Many factors may contribute to this situation. Most common being the misdiagnosis with TB due to striking radiological similarity between ABPA and TB, and the patient goes on receiving anti-TB drugs for long periods. In some Indian studies, ABPA was misdiagnosed as TB in as high as 17% to 50% cases. Corticosteroids are grossly misused in asthmatics in our country which further minimizes the chances to diagnose ABPA among early stages. The mycoserological tests and investigations like CT scan required for diagnosing ABPA are not widely available and are rather expensive. Apart from this there is lack of awareness about ABPA in general practitioners, medical specialists and many chest specialists.

Pathogenesis

Human beings acquire infection with Aspergillus species by inhalation of the airborne spores of the fungus. The spores of Aspergillus are 2 to 3 µm in size and can reach the alveoli when inhaled. After reaching the airways the spores germinate. The exact pathogenesis of ABPA is poorly understood. There is no correlation between the intensity of spore exposure and rate of sensitization to the fungus as determined by skin testing. Inhalation of fungal spores in atopic individuals can manifest in the two following forms: (a) an asthma-like reaction on transient exposure to high intensity of Aspergillus spores with IgE-mediated reaction and eosinophilic inflammation; (b) an asthmatic reaction to Aspergillus fungi colonized in the airways resulting in IgG- and IgE-mediated immune response. There are Th2-mediated and IL-8-mediated response resulting in eosinophilic and neutrophilic inflammation, respectively. In conjunction, the immunologic inflammatory responses and mycotoxins and proteolytic enzymes released by the fungi lead...
Table 1: Criteria for the diagnosis of ABPA (patients without cystic fibrosis)

1. Asthma
2. Immediate cutaneous reaction to A. fumigatus
3. Total serum IgE concentration (>1000 ng/ml)
4. Elevated A. fumigatus-specific serum IgE levels
5. Precipitating antibodies to A. fumigatus in the serum
6. Peripheral blood eosinophilia (not essential for diagnosis)
7. Chest Roentgenographic infiltrates (not essential for diagnosis)
8. Central bronchiectasis

Clinical Features

In patients with asthma, the clinical features of ABPA range from mild asthma to severe, predominantly central bronchiectasis. In ABPA, exacerbations are characterized by episodes of increasing dyspnea, cough with sputum production, pleuritic pain and fever. The sputum of the patients may consist of brownish mucous plugs and hemoptysis is rare. Examination reveals rhonchi and wheezing on auscultation of the chest during acute exacerbation. Some patients of ABPA may have minimal symptoms whereas radiographic changes of ABPA are present. Laboratory examination in ABPA may reveal peripheral blood eosinophilia. Total serum IgE is often >1000 ng/ml along with elevated levels of AF-specific serum IgE levels and presence of precipitating antibodies to AF. Patients with ABPA demonstrate immediate skin reactivity to the AF antigen. Spirometry shows airflow obstruction, which responds to steroids. If left untreated, ABPA can lead to severe bronchiectasis and fibrosis leading to fall in vital capacity and forced expiratory volume in 1 second (FEV1).

Diagnosis

ABPA occurs mainly in asthmatics and patients with cystic fibrosis. In asthmatic patients, the diagnosis of ABPA is based on the presence of a combination of clinical, biological and radiological criteria. The prevalence of ABPA is difficult to establish, however it ranges between 1 and 2%. If clinical suspicion for ABPA exists, laboratory and imaging studies should be obtained to establish the diagnosis. Sputum culture for Aspergillus may also be done. A minimum of five criteria are required to establish the diagnosis of ABPA. The criteria are outlined below. Eight criteria for ABPA diagnosis were initially identified, but only some of them are essential. The non-essential criteria, for example, pulmonary infiltrates or blood eosinophilia may be only present at the time of exacerbation or during the acute phase of the disease. Bronchiectasis, involving the more central segmental bronchi is a strong diagnostic criterion but is not always present in patients during follow-up and at the time of diagnosis.

In cystic fibrosis patients, ABPA is a common complication, occurring in approximately 10% of cases. As several of the criteria used for ABPA diagnosis are common manifestations of cystic fibrosis it is difficult to establish diagnosis of ABPA in cystic fibrosis patients. Many a times, Cystic fibrosis patients have exacerbations with bronchial obstruction, pulmonary infiltrate and bronchiectasis. To add to the diagnostic dilemma, cystic fibrosis patients may have immune responses to Aspergillus (IgE, IgA, IgG antibody production and elevated total serum IgE levels), in the absence of ABPA. The boundary separating these responses from those involved with ABPA is difficult to define.

Recently, the Cystic Fibrosis Foundation has proposed a new set of criteria for ABPA diagnosis in cystic fibrosis patients:

1. Clinical deterioration (coughing, wheezing, increased sputum production, exercise intolerance and decrease in pulmonary function);
2. Immediate hypersensitivity to A. fumigatus (positive skin test or IgE response);
3. Total serum IgE concentration >1000 kUI/L;
4. Precipitating antibodies to A. fumigatus;
5. Abnormal chest roentgenogram (infiltrate, mucus plugs or unexplained changes compared to previous chest X-ray).

Stages of ABPA

The natural history of ABPA is poorly characterized and is difficult to predict. Patterson and co-workers described five stages of ABPA based on clinical presentation and the staging is useful in the management of patients. The staging does not reflect progression of disease.

Stage I—Acute: Patients are diagnosed with ABPA after
meeting the diagnostic criteria outlined above. In the acute stage, the levels of serum IgE and IgG specific to AF are elevated. While peak levels of IgE are noted, IgE specific to AF may lag behind by 12 to 16 weeks. Radiographically, infiltrates in the upper and middle lobes may be seen. Patients in stage I respond well to oral corticosteroids with resolution of symptoms, radiographic changes, and significant reduction in IgE levels.

**Stage II — Remission**: Patients are considered to be in stage II when resolution of stage I findings persist for 6 months or longer while they are off corticosteroids. Serum IgE levels are often in the normal range or slightly elevated. The chest radiograph may show complete resolution of infiltrates. Patients may remain in stage II for an indefinite period of time or symptoms may recur leading to stage III.

**Stage III — Exacerbation**: Relapse of symptoms, occurrence of new infiltrates on chest radiograph, or rising IgE levels following stage II indicate exacerbation, otherwise referred to as stage III. Patients require treatment for ABPA as discussed below.

**Stage IV — Corticosteroid-dependent asthma**: In this stage, patients have persistent symptoms of productive cough and wheezing and often have radiographic changes. Patients continue to have symptoms and elevated levels of IgE despite being on oral corticosteroids. Their symptoms get worse if corticosteroids are withdrawn.

**Stage V — End stage**: Patients with ABPA whose diagnosis was missed in early stages, and had received treatment only for asthma with short courses of steroids, bronchodilators, and antibiotics, may progress to bronchiectasis, cavitary changes, and fibrosis. Even patients in stage V have shown response to oral corticosteroids. Lee and co-workers reported a greater 5-year survival in stage V if their post-bronchodilator FEV1 was more than 0.8 L.

**Radiology and Pulmonary Function Tests**

Radiologic changes in ABPA can be classified as acute or chronic changes. Chronic changes are a sequel of the repeated attacks of acute illness and are often associated with permanent physiologic impairment.

**Acute Changes**: Most common abnormalities involve the parenchyma and manifests in about 80-90% of patients as ill-defined homogenous radiological shadows, without the evidence of volume loss, they may be limited or massive in their extent. The shadows may involve any part of lung although the upper lobes involvement is most commonly reported. The most characteristic feature of these shadows is that they resolve after expectoration of a mucus plug but tend to recur at the same or some other location (that is why known as ‘fleeting shadows’). Half of the shadows leave permanent residue known as ‘ring shadows’. It is the obstruction by the mucus plugs that obstructs the lumen and cast homogenous opacities on chest X-ray.

Bronchial abnormalities occur in 50-70% of acute episodes of ABPA. The radiology reveals tramline, parallel line or ring shadows and (represents normal or abnormal bronchial wall) “toothpaste” and gloved “finger shadows” (represents intrabronchial exudate). Tramline shadows are the thickened wall of undilated bronchi, so that the distance between the walls is that of a normal bronchus. Parallel lines are the wall of bronchiectatic airways, the distance between the walls is greater than the normal. Ring shadows are bronchiectatic airways seen en face or small abscesses. When a normal or bronchiectatic segment gets filled with exudate, tramline or parallel line shadows change to toothpaste or gloved finger shadows, and obviously the removal of intrabronchial exudates will cause reversal of the shadows.

In 15-30% of patients with ABPA mucoid impaction of the bronchi occurs. When this mucoid impaction involves the large bronchus and extends into the second, third or fourth order bronchi toothpaste shadows results while the involvement of several second order bronchi leads to gloved finger appearance which are identified as tubular radio-densities 2-3 cm long and 5-8 cm wide branching distally from the hilum and filled with inflammatory exudate.

Peri-hilar radio-densities occur in 40% episodes of ABPA and mimics hilar adenopathy. Other acute changes include air-fluid levels (10-20%), diffuse nodulation (10-20%), avascular areas (10%), and signs of hyperventilation (10-30%). Pleural effusion is rare with around 5% presenting with the same.

**Chronic Changes**: Chronic changes are a sequel of repeated acute episodes. The upper lobe is usually involved in chronic ABPA and shows fibrotic changes. The incidence of pulmonary fibrosis varies from 0-20% in patients with ABPA. Pulmonary fibrosis, pneumothorax and cavities occur during end-stage ABPA.

Central bronchiectasis is also a characteristic feature of ABPA. Central bronchiectasis involves small bronchi and bronchioles. In ABPA central bronchiectasis occurs as Aspergillus grows only in relatively large bronchi (second, third and fourth order) with localized damage to bronchial wall sparing small bronchi.

In 30-40% patients of ABPA High Resolution Computed
Tomography (HRCT) is able to detect the central bronchiectasis. One study showed that HRCT scan is more sensitive than radiography for diagnosing bronchiectasis.57 In this study, bronchiectasis was identified in 14/17 ABPA patients (82%), pleural thickening in 14 (82%) and atelectasis in 9 (64%).57

Respiratory function tests (expiratory flow rates, lung volumes and diffusion capacities) are useful for diagnosis and during follow-up, but alone are not sufficient for monitoring treatment. Obstruction and restriction are both aggravated during acute exacerbations. Reductions in lung volume and diffusing capacity have been observed during exacerbations. Treatment for ABPA. The lung function levels of more than 100% above the base-line value indicate that the patient is at high risk for an exacerbation. The lung function after treatment for the acute phase of ABPA is often normal or improved, but always remains reduced in some patients. It also improves the clinical status of corticosteroid-dependent ABPA patients without any toxic effects.

Treatment
The goals of the treatment are:
1. To limit exacerbations or acute symptoms of ABPA
2. To eradicate colonization and/or proliferation of A. fumigatus in lumens with bronchiectasis and mucus plugs
3. To manage symptoms of asthma and
4. Prevention of permanent lung damage

Therapy includes the following: (1) Anti-inflammatory—oral corticosteroids; (2) Antifungal—Itraconazole; (3) Bronchodilators; (4) Bronchial hygiene.

Oral Corticosteroids
Systemic corticosteroids are currently the most effective treatment for the acute phase of ABPA as they suppress the immunologic reaction and the inflammatory response, leading to peripheral eosinophilia, elevated IgE levels, bronchial inflammation, hyperreactivity, sputum production, bronchospasm, wheezing, and radiographic changes. The recommended dose is 0.5 mg/kg/day for the first 2 weeks, followed by a progressive decrease in dose over the next 6–8 weeks. The treatment is monitored by assessing symptoms (fever, chest pain, hemoptysis, acute wheezing and sputum production), however, monitoring must also include a chest roentgenogram or HRCT scan, as infiltrates do not lead to clinical manifestations in a third of cases.69 Increases in total IgE serum levels of more than 100% above the base-line value indicate that the patient is at high risk for an exacerbation. The lung function tests recommended for asthma patients must also be performed as reductions in lung volume, diffusing capacity or exercise intolerance may be associated with an exacerbation.

Long-term systemic corticosteroid therapy is not recommended and thus assessment of these parameters is necessary for monitoring the treatment. If the patient has no new exacerbation within 6 months, he is judged to be in remission (stage II). Stage IV patients have severe asthma, which is corticosteroid-dependent. In these cases, the minimal dose required to stabilize the patient must be identified. The extent of the bronchial destruction in stage V patients makes the prognosis poor. In addition, these patients suffer from recurrent infections (the majority of which involve Pseudomonas) and respiratory insufficiency with limited exercise tolerance. Treatment with corticosteroids is generally proposed, but is poorly efficient.

Antifungal Drugs
Several antifungal agents (e.g. amphotericin B, ketoconazole, clotrimazole, nystatin and natamycin) have been proposed as treatments for ABPA. However, no significant beneficial effects were observed when these drug treatments were tested and in several cases these agents were responsible for severe adverse effects.64 In contrast, the new orally administered antifungal agent, Itraconazole, appears to be an effective adjunctive therapy for ABPA. The results of a 16-week randomized double-blind trial of twice daily treatment with either 200 mg Itraconazole or placebo, showed that Itraconazole prevented disease progression in corticosteroid-dependent ABPA patients without any toxic effects.65 A positive response was defined as a reduction of at least 50% in corticosteroid dose, a decrease of at least 25% in serum IgE concentration, and one of the following: an improvement of at least 25% in exercise tolerance or pulmonary-function tests or the partial clearance or absence of pulmonary infiltrates. These results indicate that Itraconazole could be used as a adjunctive treatment for ABPA. Meta-analysis of the data available (mainly three prospective, randomized and controlled studies) led to the conclusion that Itraconazole modifies the immunologic activation associated with ABPA and improves clinical outcome, at least over a period of 16 weeks (Cochrane Airways Group Asthma Trials Register).66 Adrenal suppression caused by the inhalation of corticosteroids and Itraconazole treatment is a potential concern. On the one hand, treatment with this antifungal agent reduces bronchial inflammation and may prevent bronchial destruction and exacerbation in stable ABPA patients. It also improves the clinical status of corticosteroid-dependent ABPA patients.

Table 2: The common radiological abnormalities with their approximate frequency of occurrence

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<th>Abnormality</th>
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<td>100</td>
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<tr>
<td>Homogeneous Shadows (Fleeting infilrates)</td>
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<td>15</td>
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<tr>
<td>Gloved finger Shadows</td>
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Fig. 3: Mucus plugging and ground glass opacities

Tomography (HRCT) is able to detect the central bronchiectasis. One study showed that HRCT scan is more sensitive than radiography for diagnosing bronchiectasis.57 In this study, bronchiectasis was identified in 14/17 ABPA patients (82%), pleural thickening in 14 (82%) and atelectasis in 9 (64%).57

Respiratory function tests (expiratory flow rates, lung volumes and diffusion capacities) are useful for diagnosis and during follow-up, but alone are not sufficient for monitoring treatment. Obstruction and restriction are both aggravated during acute exacerbations. Reductions in lung volume and diffusing capacity have been observed during exacerbations and in patients with end-stage ABPA. The severity of the obstruction in corticosteroid-dependent asthma (stage IV) varies depending on the patient.56,61,64 Deterioration of lung function also differs between ABPA patients; in some individuals lung function remains stable, whereas in others functional parameters progressively deteriorate in manner that is associated with the pattern of obstruction and restriction.62

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ABPA patients. On the other hand, long-term prescription of an antifungal therapy may lead to resistance. The trials validating the use of Itraconazole in ABPA patients used a dose of 200 mg/day, administered for a duration of 16 weeks.\(^5\) Fiberoptic bronchoscopy may be necessary to remove the mucoid impaction responsible for atelectasis in rare cases where it is refractory to corticosteroid treatment.

In addition to corticosteroids and Itraconazole, bronchial hygiene to improve airway clearance and inhaled bronchodilators to reduce bronchospasm are recommended. Consideration for pneumococcal vaccine and annual influenza vaccination should be included in the management.

Prognosis

The prospective population based studies of the outcome of the patients with ABPA are lacking. Some patients with ABPA progress to end-stage pulmonary fibrosis with cor pulmonale while others maintain almost stable pulmonary function tests for years altogether. Malo and co-workers found that after 5 year asthmatic patients with ABPA have more compromised pulmonary physiologic tests than did asthmatic patients without ABPA. Both groups (asthmatics with or without ABPA) had features of asthma (decreased flow rates and increased lung volumes), but asthmatics with ABPA tended to exhibit decreased diffusing capacity and total lung capacity. This is in accordance with superimposition of a restrictive defect (pulmonary fibrosis with bronchiectasis) on a pre-existing obstructive defect (asthma).

Conclusion

In conclusion, ABPA is a common manifestation in chronic allergic asthma and cystic fibrosis patients. Despite the high frequency of the disease among these patients, diagnoses are not generally made until a long time after the initiation of the asthmatic disease. When the clinical, radiological and biological criteria for ABPA appear in combination and the diagnosis is made, a treatment that includes both corticosteroids and the antifungal agent, Itraconazole, needs to be administered. However, the treatment regimens for this antifungal therapy have yet to be definitely established.

Practical Approach for Diagnosing ABPA in the Clinic

- In patients with poorly controlled asthma, characteristic radiographic changes or when there is a frequent history of bronchitis/pneumonia, suspect ABPA.
- In patients with CF, when new infiltrates appear with wheezing and worsening of clinical course, suspect ABPA. Annual serum IgE testing is recommended.
- When ABPA is suspected, check for total IgE levels total as well as IgE specific for Aspergillus species and perform skin testing for Aspergillus species for immediate hypersensitivity type reaction.
- If these are positive or suggestive of ABPA, perform HRCT of the chest to evaluate for central bronchiectasis.

References

24. Kumar R, Gaur SN. Prevalence of allergic bronchopulmonary


