CLINICAL ASPECTS OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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1. ABSTRACT

Allergic Bronchopulmonary Aspergillosis (ABPA) is characterized by recurrent pulmonary infiltrates that can result in central bronchiectasis and bronchiolitis obliterans especially if there is a lack of recognition and treatment. The incidence of ABPA is 1-2% in patients with persistent asthma and approximately 7% (range 2-15) in patients with cystic fibrosis. The diagnostic criteria are useful in that there is no single test (with the exception of central bronchiectasis in patients with asthma) that identifies ABPA. The differential diagnosis of ABPA includes many conditions including chronic eosinophilic pneumonia, Churg Strauss Syndrome, Hyper-IgE Syndrome, persistent asthma with lobar collapse, and cases of parasitism. The most useful laboratory assays in patients who have immediate cutaneous reactivity to Aspergillus mixtures or A. fumigatus are total serum IgE concentration, elevated serum IgE-A.fumigatus and serum IgG-A.fumigatus. Prednisone remains the drug of choice yet need not be administered indefinitely.

2. INTRODUCTION

The incidence of allergic bronchopulmonary aspergillosis (ABPA) is about 1-2% in patients with persistent asthma (1) and from 2-15% in patients with cystic fibrosis (2-16). Some patients with chronic granulomatous disease or hyper-IgE syndrome either have ABPA or features of an overlap condition that resembles aspects of ABPA (17). Scattered cases of concomitant ABPA and allergic fungal sinusitis are being reported (18-19) but most patients with ABPA do not have allergic fungal sinusitis. ABPA can be classified as to the presence or absence of bronchiectasis (20) based on high resolution CT examinations and also into one of 5 stages: acute, remission, recurrent exacerbation, corticosteroid dependent asthma, and end-stage fibrocavitary disease (21). Prednisone administration remains the drug of choice but need not be administered indefinitely.

3. DIAGNOSTIC CRITERIA OF ABPA IN ASTHMA AND CYSTIC FIBROSIS

The classic case of ABPA has many features that co-exist with allergic asthma. The use of a series of characteristics has been useful in identifying cases of ABPA in patients with asthma and are presented in Table 1. Diagnostic criteria for patients with cystic fibrosis are presented in Table 2 based on a Consensus Conference of the Cystic Fibrosis Foundation (22). In patients with asthma, the patient with classic ABPA will have all or nearly all the diagnostic criteria listed in Table 1 including central bronchiectasis as shown in Figure 1, elevated total serum IgE concentration, and immediate cutaneous reactivity to Aspergillus fumigatus or a mixture of Aspergillus species. If tested, such patients also will demonstrate elevated isotypic antibodies to A. fumigatus of the IgE, IgG and IgA classes (24, 25). Some patients with asthma have ABPA but do not have detectable central bronchiectasis by high resolution computerized tomography (20). These patients do have recurrent pulmonary infiltrates but appear to have a less aggressive form of ABPA. Nevertheless, the serologic response is
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**Table 1. Diagnostic Criteria of Allergic Bronchopulmonary Aspergillosis**

<table>
<thead>
<tr>
<th>Classic Case with Bronchiectasis in a Patient with Asthma</th>
<th>Minimal Essential Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest roentgenographic infiltrates</td>
<td>No</td>
</tr>
<tr>
<td>Central bronchiectasis (inner 2/3 of CT field)</td>
<td>Yes</td>
</tr>
<tr>
<td>Immediate cutaneous reactivity to Aspergillus species</td>
<td>Yes (or in vitro positive)</td>
</tr>
<tr>
<td>Total serum IgE &gt; 417 kU/L (&gt;1000 ng/mL)</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum precipitating antibodies to Aspergillus fumigatus</td>
<td>No</td>
</tr>
<tr>
<td>Peripheral blood eosinophilia</td>
<td>No</td>
</tr>
<tr>
<td>Elevated serum IgE-A.fumigatus and or IgG- A.fumigatus</td>
<td>No (but will be positive in most cases)</td>
</tr>
</tbody>
</table>

**Table 2. Diagnostic Criteria in Cystic Fibrosis**

**Classic Case of ABPA**
- Clinical deterioration (cough, wheezing, exercise intolerance, change in pulmonary function, increased sputum)
- Total serum IgE concentration > 1000 kU/L
- Immediate cutaneous reactivity to Aspergillus or in vitro presence of serum IgE-A.fumigatus
- Precipitating antibodies to A. fumigatus or serum IgG-A.fumigatus by an in vitro test
- Abnormal chest roentgenogram (infiltrates, mucus plugging or a change from a previous film)

**Minimal Diagnostic Criteria**
- Clinical deterioration (cough, wheezing, exercise intolerance, change in pulmonary function, increased sputum)
- Total serum IgE concentration >500kU/L
- Immediate cutaneous reactivity to Aspergillus or in vitro presence of serum IgE-A.fumigatus
- and one of the following
  - Precipitating antibodies to A. fumigatus or serum IgG-A.fumigatus by an in vitro test
  - Abnormal chest roentgenogram (infiltrates, mucus plugging or a change from a previous film)

**Suggestions for Screening for ABPA**
- Maintain a high level of suspicion after age 6 years
- Obtain a total serum IgE concentration annually. If it is > 500 kU/L, determine immediate cutaneous reactivity to Aspergillus or by in vitro test for IgE-A.fumigatus
- If the total serum IgE is <500 kU/L, repeat the determination if the clinical suspicion is high such as with a disease exacerbation. Screen by the total serum IgE concentration annually

**Figure 1.** A 43 year old female with asthma and ABPA. The axial view from the high resolution CT of the lung at the level of the carina demonstrates multiple areas of bronchial wall thickening and central (proximal) bronchiectasis. The open triangle identifies an area of bronchiectasis in the left mid lung. Bronchiectasis also is present on the right and small cystic areas are present in the right anteriorly.

consistent with ABPA but the mean total serum IgE concentration in 28 patients without bronchiectasis was 2776 kU/L compared with 4950 kU/L in 58 patients with ABPA where bronchiectasis was present (20). The serum IgE-Af antibodies were 4.06 times sera of patients with asthma with 3 or 4+ immediate cutaneous reactivity to Aspergillus but

without sufficient criteria for a diagnosis of ABPA. This ratio was 4.78 in ABPA patients with bronchiectasis (20). For serum IgG-Af, the patients without bronchiectasis had ratios of 3.62 compared with 7.78 for patients with bronchiectasis (20). These findings emphasize that the true differential diagnosis is patients with asthma who have immediate cutaneous reactivity to Aspergillus species as opposed to sera from non-atopic subjects or non-asthma patients. Making the diagnosis of ABPA in patients with cystic fibrosis may be difficult but major reductions in FEV₁ or the new onset of intermittent wheezing in the setting of patients who produce A.fumigatus repeatedly in sputum may be tip-offs. The criteria proposed by the Cystic Fibrosis Foundation Consensus Conference are presented in Table 2. When patients with Cystic Fibrosis are screened with annual or semi-annual phlebotomies, obtaining the total serum IgE concentration and a test for in vitro IgE antibodies to A.fumigatus may provide useful information to lead to a diagnosis of ABPA. If the total serum IgE concentration is > 500 kU/L, then additional tests such as skin testing for immediate reactivity to Aspergillus or in vitro testing for IgE antibodies to A. fumigatus should be obtained.

Alternative criteria for the diagnosis of ABPA in cystic fibrosis as proposed by the Epidemiologic Study of Cystic Fibrosis were as shown in Table 3.

When these criteria were applied to 14,210 patients with cystic fibrosis in the United States and
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Table 3. Alternative Diagnostic Criteria in Cystic Fibrosis

Two of three criteria required
- Immediate cutaneous reactivity to A. fumigatus
- Precipitating antibodies to A. fumigatus
- Total serum IgE concentration >1000 kU/L

And at least two of the following:
- Bronchoconstriction
- Peripheral blood eosinophilia >1000/µL
- History of pulmonary infiltrates
- Elevated serum IgE A. fumigatus or IgG-A. fumigatus
- Fumigatus in sputum by smear or culture
- Response to steroid treatment

Based on the Epidemiologic Study of Cystic Fibrosis (4)

Table 4. Additional Alternative Diagnosis Criteria in Cystic Fibrosis

- Four required criteria
- Immediate cutaneous reactivity to A. fumigatus
- Total serum IgE concentration > 1000 kU/L
- Multiple serum precipitins to A. fumigatus
- Physician suspicion of ABPA based on at least one of the following:
  - Reversible bronchospasms or asthma
  - Pulmonary infiltrates
  - Peripheral eosinophilia > 1000/µL
  - Fumigatus in sputum or hyphae on smear
- Response to inhaled or oral corticosteroids

Based on the Epidemiologic Registry of Cystic Fibrosis (26)

Canada, who were over 4 years of age, 282 (2%) patients had sufficient criteria for the diagnosis of ABPA (4). Some 11% of all the patients had been found to have wheezing on examination in the previous 6 months, a number lower than anticipated. Sputum harboring Pseudomonas spp had occurred in the previous year in 62% of the patients (4). In the cohort of patients with ABPA and cystic fibrosis, wheezing that was physician-documented had been present in 17% of patients and a diagnosis of asthma had been made for 30% of patients (4). Seventy-three percent of the ABPA patients had sputum containing Pseudomonas spp (4). A. fumigatus had been identified in sputum in 34% of the ABPA patients compared to 8% of the cystic fibrosis patients without ABPA. Somewhat different criteria were used in the Epidemiologic Registry of Cystic Fibrosis, a study of 12,447 patients in 9 European countries (26). The criteria for the diagnosis of ABPA were as shown in this series in table 4; ABPA was identified with these criteria in 7.8% of patients with a country range of 2.1-13.6% however (26). The ABPA patients were more likely to be colonized with A. fumigatus (45% vs 16.2% in patients without ABPA). Of note was that there was a trend toward increased recoveries of other bacteria or fungi in sputum from ABPA patients with cystic fibrosis than patients with cystic fibrosis alone (26). This finding applied to P. aeruginosa (84.5 vs 64.1%), B. cepacia (7.9 vs 5.7%), S. maltophilia (16.7 vs 7.3%), and C. albicans (50.6 vs 37.3%).

4. SYMPTOMS OF ABPA

Patients may present with symptoms of cough, dyspnea, wheezing (including status asthmaticus), sputum plug production, low grade temperature along with symptoms of seasonal or perennial allergic rhinitis. Alternatively, patients may have no respiratory symptoms even at the time of pulmonary infiltrates present on chest roentgenograms or they may have a mild sense of dyspnea or non-productive cough despite having a collapsed lobar segment or lung. In fact, in ABPA, when there is a new pulmonary infiltrate associated with eosinophilia and a lobar segment is affected, a comparable radiologic pattern associated with S. pneumoniae pneumonia would cause a higher temperature elevation along with rigors and chest pain. In ABPA, the same radiologic pattern typically would be associated with few to no symptoms. In some cases, the new infiltrate is recognized because of an asymptomatic 20% decline of FEV1 or when a chest roentgenogram is obtained for another indication.

When ABPA has resulted in significant areas of bronchiectasis or pulmonary fibrosis, there may be daily purulent sputum production that may reveal P. aeruginosa, S. aureus, A. fumigatus, combinations of bacteria or atypical mycobacteria (27). Patients with end-stage pulmonary fibrosis from ABPA have experienced pneumothoraces (28), clubbing, cyanosis, and require home oxygen (29, 30).

Patients with ABPA can be expected to have other atopic conditions such as allergic rhinitis, atopic dermatitis, and drug allergies (30) so that associated symptoms may be present. Some patients have chronic sinusitis where there is colonization of sinuses and bronchi by P. aeruginosa. A small number of patients have pan-sinusitis and nasal polyps and are found to have both ABPA and allergic fungal sinusitis (31, 32). Their symptoms are explained by sinus headaches and purulent nasal drainage or loss of olfaction and inability to produce nasal secretions.

Patients with ABPA and cystic fibrosis may have a recent diagnosis of asthma and intermittent bouts of wheezing comparable to persistent or intermittent asthma. ABPA patients have been reported to have an FEV1% about 10% lower than cystic fibrosis patients without ABPA (26). In the same study, in patients with FEV1 from 40-70%, the incidence of ABPA was 12.1% compared to an incidence of 6.6% if the FEV1 was >70% (26). Similar data were found for the frequency of ABPA in patients with cystic fibrosis whose FEV1 was <40%.

5. STAGING OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA can be classified according to a system initially published in 1982 (21) which combines the chest roentgenogram, presence of CT findings, severity of asthma and overall respiratory status. Stage I (Acute) describes patients with “classic” ABPA who have chest roentgenographic infiltrates (typically of upper lobes or the middle lobe), persistent asthma, and immediate cutaneous reactivity to Aspergillus mixtures used in skin testing or A. fumigatus, elevated total serum IgE concentration (>417 kU/L), precipitating antibodies to A. fumigatus, and central (proximal bronchiectasis). These patients will have peripheral blood eosinophilia and increased levels of serum IgE A. fumigatus and or IgG A. fumigatus compared to sera...
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from patients with asthma and 3 or 4+ immediate skin tests to Aspergillus mixes used for prick skin testing. The total serum IgE concentration is increased and in one series ranged from 352.5-29,167 kU/L (33). High resolution CT examinations reveals cylindrical, saccular or varicose bronchiectasis that in ABPA or ABPA with cystic fibrosis is located in upper lobes or the middle lobe (34-37). There may be mucus plugging not visualized on the chest roentgenograms. An important aspect of the diagnosis of patients with ABPA- Stage 1 is the response to prednisone administration (38). The chest roentgenograms typically clear by 1-2 months after a moderate prednisone dose of 0.5 mg/kg/day for 2 weeks and then the same dose administered for 2 months on alternate days. The total serum IgE concentration declines by 33% over a 6 week period (38). Failure to find radiographic clearing and a drop in total IgE concentration suggests a new ABPA episode or non-compliance with medications. To summarize, in the Acute stage of ABPA, the response to prednisone results in radiographic clearing or returning to baseline chest roentgenogram status, improvement in respiratory symptoms and function and decline in the total serum IgE concentration at least by 33%.

If a patient has received prednisone and improved, there can be tapering and discontinuation of prednisone. Asthma medications such as inhaled corticosteroids and bronchodilators may be required, but if the prednisone can be discontinued for at least 6 months without recurrence of chest roentgenographic or high resolution chest tomographic evidence of new infiltrates, the patient is considered in Stage 2 or Remission (21,33). Some patients experience permanent remissions. The range of total serum IgE concentrations in 7 patients in Stage 2 who had not received prednisone for at least 1 year was from 123 - 945 kU/L (33). Some patients had elevated serum IgE-A. fumigatus and IgG-A. fumigatus antibodies in the ABPA range and others did not (33). When patients have reached Remission, serial total IgE concentrations should be obtained less often, such as every 2-3 months initially, so that a baseline range has been established which can be used for future comparison should an asymptomatic exacerbation occur.

When there are new pulmonary infiltrates with at least a 100% increase in the total serum IgE concentration, the patient is classified into Stage 3 or Recurrent Exacerbation (21,33). There may be peripheral blood eosinophilia and no other cause of the chest roentgenographic infiltrates such as community acquired pneumonia. Administration of prednisone as for Stage 1 patients again results in clearing of the chest roentgenographic infiltrates and decline in the total serum IgE concentration. The IgE concentration is not necessarily in the normal range, and prednisone should not be continued in an attempt to lower this concentration to the normal of adults of 125 kU/L. In a patient, the pulmonary infiltrate and ABPA exacerbation had a total serum IgE concentration of 6000 kU/L with a Remission concentration of 3600 kU/L, still a markedly high value. When another pulmonary infiltrate occurred, the total serum IgE concentration was 14,583 kU/L followed by a Remission concentration of 4430 kU/L and another Exacerbation concentration of 13,029 kU/L (33). Nearly all patients will have elevated serum IgE-A. fumigatus and or IgG-A. fumigatus antibodies during Recurrent Exacerbations. Precipitating antibodies may or may not be present. Many patients with ABPA are identified when they are in Recurrent Exacerbation Stage as there have been previous infiltrates which in some cases had been misdiagnosed as community acquired pneumonias, lobar or segmental pulmonary collapse from mucus plugging from acute asthma episodes. Sputum plugs may be expectorated but some patients have recurrent exacerbations without any sputum production.

For some patients, it is impossible to manage the asthma without prednisone despite allergen avoidance, high dose inhaled corticosteroids and other medications. Such ABPA patients are classified into Corticosteroid Dependent Asthma or Stage 4 (21,33, 39). In a series of 17 patients with Stage 4 ABPA, the total serum IgE concentrations varied widely from 115-5370 kU/L (33). The serum IgE-A. fumigatus and IgG-A. fumigatus values may be elevated or normal. New radiographic infiltrates may occur especially if the prednisone dose is <30 mg on alternate days. ABPA appears to cause a worsening in the course of asthma at least for these patients because the dose of prednisone, used as a proxy for the severity of asthma, is greater after the diagnosis of ABPA has been made (39). The chest roentgenograms may be within normal limits or show varying degrees of pulmonary fibrosis or bronchiectasis. Sputum may or may not be expectorated.

Often because of a failure to diagnose and treat ABPA, patients may present with irreversible airways obstruction or restrictive lung findings and a partial or no satisfactory response to prednisone and other anti-asthma medications. This condition is designated as End Stage Fibrocavitary ABPA or Stage 5 (21, 40). New radiographic infiltrates are infrequent and may be from bacterial infections as opposed to ABPA exacerbations. The respiratory status ranges from mild to severe or end stage requiring home oxygen. The range of total serum IgE concentrations is from 150-10,417 kU/L (40). Most patients still have elevated serum IgE-A. fumigatus and or IgG-A. fumigatus antibodies which may be useful in identifying cases where the patient has asthma and pulmonary fibrosis. Lung biopsies may show areas of eosinophilic pneumonia, mucoid impaction syndrome, interstitial fibrosis with granulomas or granulomatous bronchiolitis. Chest roentgenograms may demonstrate cavities, a mycetoma in a cavity, bronchiectasis, volume loss, bullous changes and chronic interstitial infiltrates (40). If the FEV\textsubscript{1} after prednisone treatment remains severely decreased, such as under 0.8 L, the prognosis is poor (40). Some patients may be candidates for lung transplantation but in a patient with ABPA and cystic fibrosis, transplantation of a brother’s lung resulted in recurrence of ABPA in the donor lung (41).

Patients with ABPA Stages 1-5 all have central bronchiectasis which is bronchiectasis in the inner 2/3 of the lung fields on axial sections of the CT examinations (37). Some patients have ABPA without bronchiectasis and
are designated as ABPA-S for seropositive (20). Such patients may have pulmonary infiltrates (20, 42) but have a less aggressive form of ABPA (20). While bronchiectasis is not present, collapse or consolidation was found in 20% of ABPA-S patients compared to 75% of ABPA-CB patients (42). Mucous plugging was present in none of the ABPA-S patients but was found in 63% of ABPA-CB patients (42).

The serologic tests such as total serum IgE concentration and serum IgE-A. fumigatus and IgG-A. fumigatus are helpful in diagnosis (20). It has been argued that ABPA-S is not really ABPA because bronchiectasis is not present. However, the counter-argument is that such patients may and do develop bronchiectasis if recurrent infiltrates are not identified and treated. Induced sputum from ABPA-CB patients as compared to ABPA-S patients demonstrates greater numbers of eosinophils (8.4% vs 2.4% vs 1.8% in A. fumigatus sensitized patients with asthma) and neutrophils (60.3% vs 34.5% vs. 50.3% in A. fumigatus sensitized patients with asthma (42). Sputum eosinophil cationic protein was much higher in ABPA-CB (13, 706 ng/mL) compared to ABPA-S (1634 ng/mL), A. fumigatus sensitized patients with asthma (1551 ng/mL) and non-A. fumigatus sensitized patients with asthma (309 ng/mL) (42). These findings are consistent with an increased level of inflammation in patients with ABPA-CB.

6. LABORATORY FINDINGS IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSI

In screening for ABPA, an approach is to use a very sensitive test such as immediate cutaneous testing with reactive Aspergillus mixes or A. fumigatus followed by a highly specific test battery, that of the total serum IgE concentration and serum IgE-A. fumigatus and IgG-A. fumigatus. The initial screening test is the percutaneous or prick test which is positive in nearly all ABPA patients (a few require intradermal injections) and in 20-25% of patients with persistent asthma (36, 43). Nevertheless, skin test reactivity varies greatly with commercially available extracts (44). The 3 test battery, which may be expanded to 4 tests including precipitins to A. fumigatus, have a very high level of specificity should they be negative or not in the range of ABPA. An alternative approach is to obtain serum IgE-A. fumigatus by ELISA or RAST with followup determinations with the 3 or 4 test battery. A crucial control not found commercially is that sera from patients with asthma who have 3 or 4+ positive reactions upon immediate cutaneous testing are used to compare the unknown and possibly ABPA sera to. For example, at a 1:100 dilution in the IgE-A. fumigatus assay, the optical density of sera from asthma patients who do not have ABPA is approximately 5 times greater than non-atopic sera. ABPA sera is at least double and may be >10 fold higher than asthma sera or perhaps >50 fold non-atopic sera at the 1:100 dilution (43,45). There is a difference between commercially obtained ELISA or RAST tests for A. fumigatus antibodies which compares sera to non-atopic controls and the more specialized determinations that help distinguish ABPA from patients with asthma who have immediate cutaneous reactivity to Aspergillus mixes or A. fumigatus.

Screening with the total serum IgE concentration may have a place for patients with cystic fibrosis (22) where the incidence of ABPA is higher, but it does not appear to be helpful in screening for ABPA in patients with asthma. Depending on the Stage of ABPA, the total serum IgE may be very high or normal. The total serum IgE concentration can be high in patients with the combination of asthma and atopic dermatitis, in chronic eosinophilic pneumonia, Churg Strauss Syndrome, Hyper-IgE Syndrome, ABPA, parasites which cause a pulmonary response such as Ascaris lumbricoides or suum and Strongyloides stercoralis, and in some patients with Chronic Granulomatous Disease who have ABPA or a syndrome suggestive of ABPA (17).

Sputum may be present and produce hyphae of A. fumigatus but should not be expected in all patients. Indeed, in a study of the anti-fungal agent, itraconazole, patients were asked to produce sputum at the time of entry and at 16 and 32 weeks (46). From 55 patients of whom 25 had bronchiectasis, sputum samples were obtained from just 10 patients (46). Sputum analysis may have value in patients who produce sputum plugs every week which become annoying or in patients who are in Stages 4 or 5 ABPA and may have green sputum containing P. aeruginosa.

Peripheral blood eosinophilia was analyzed in 100 consecutive patients with asthma who had an immediate cutaneous reaction to A. fumigatus (47). Forty percent of asthma patients were found to have moderate peripheral blood eosinophilia (351-1000/µL) and 27% had marked eosinophilia (>1000 eosinophils/µL) (47). In contrast, moderate eosinophilia was present in 50% of ABPA patients and 20 % of ABPA patients had marked eosinophilia. These data demonstrate that patients with asthma and immediate cutaneous reactivity to A. fumigatus are likely to have >350 eosinophils/µL but peripheral blood eosinophilia is not a useful discriminating test when searching for patients with ABPA who also have asthma.

Serum precipitating antibodies (IgG) are identified in over 90% of ABPA-CB patients and in over 70% of ABPA-S patients (20). Because this test requires reactive A. fumigatus extracts and use of concentrated sera, it may be reported as negative when the sera actually have precipitins to A. fumigatus. The presence of precipitating antibodies implies a very high level of serum IgG-A. fumigatus antibodies comparable to ANA that also precipitate in systemic lupus erythematosus. Nevertheless, this test does not add greatly to the 3 other specialized determinations discussed in this Section. However, it may be useful when applied to patients who may have had skin testing or in vitro testing for IgE-A. fumigatus antibodies with poorly reactive extracts.

Sweat chloride determinations are negative in ABPA unless the patient has cystic fibrosis and ABPA (2-16). Furthermore, ABPA may be present in pancreatic sufficient patients with cystic fibrosis and may lead to a sweat test being requested. In this case, the high resolution CT may demonstrate extensive areas of both central and peripheral bronchiectasis and interstitial fibrosis to suggest the likelihood of unrecognized cystic fibrosis. ABPA
Table 5. Differential Diagnosis of Allergic Bronchopulmonary Aspergillosis

- Asthma with middle lobe syndrome or lobar collapse
- Asthma and community acquired pneumonia
- Chronic eosinophilic pneumonia
- Churg Strauss Syndrome
- Parasitism (Ascaris, Strongyloides, etc)
- Mucoid impaction syndrome
- Bronchocentric granulomatosis
- Cystic Fibrosis
- Allergic Bronchopulmonary Curvulariosis, Fusariosis, Drescleriosis, Stempyllosis, Pseudallescheriasis or Aspergillosis from other Aspergillus species
- Hyper IgE Syndrome
- Chronic Granulomatous Disease
- Idiopathic Bronchiectasis

likely fits into the” CFTR-opathies” as has been proposed (48).

Genetic studies in patients with ABPA have demonstrated heterogeneity of mutations of the CFTR (22, 26, 49). ABPA patients may express one allele for cystic fibrosis for example. It is estimated that 1/41 Caucasians carry a single mutation of delta F 508 but 4/9 ABPA patients were found to have a mutation of delta F 508 (49). Thus, carriers of an allele associated with cystic fibrosis occur in ABPA. However, in a family studied by this author where 2 of 4 children had ABPA, there were asymptomatic non-atopic carriers of delta F 508 mutations making analysis difficult.

ABPA has been associated with many other laboratory abnormalities based on tests not commercially available. Some of these include 1) bronchoalveolar lavage local production of very high amounts of IgE-A.fumigatus and IgA-A.fumigatus antibodies but not total IgE in lavage consistent with divergent locations for synthesis of allergen specific antibodies and total IgE (50), 2) activated CD3+ T lymphocytes and CD19+CD23+ B lymphocytes in peripheral blood (51), 3) increased numbers of CD86+ stimulatory B cells after incubation with IL-4 (52) suggesting that the B cells have increased sensitivity to this cytokine, 4) presence of T cell clones that react to a major recombinant allergen Asp f 2 and had features of a combined Th1/Th2 response or predominant Th2 response (53), 5) Th2 reactive clones of T cells from ABPA patients are HLA-DR2+ with alleles DRB1*1503, DRB1*1501 and DR5+allele DRB1*1104 (54), and 6) recombinant A.fumigatus allergens Asp f 2, 4 and 6 have been found to be useful in the serodiagnosis of patients with ABPA in contrast to Asp 1 and 3 (55). There are many other immunologic laboratory findings that accompany the intense immune responses to A.fumigatus in ABPA.

7. DIFFERENTIAL DIAGNOSIS OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA may be obvious in classic cases but this condition has been missed and resulted in Stage V ABPA (29). ABPA may be identified by allergist-immunologists because of screening of patients with immediate cutaneous reactivity for Aspergillus mixes or because of suspicion of a patient with asthma who has had previous community acquired pneumonias but in whom peripheral blood eosinophilia is or was present. ABPA may be identified by the pulmonologist because of the remarkable difficulty in aspirating or removing a mucus plug in a patient with asthma, whereas in a patient with cystic fibrosis without ABPA, the mucus is more readily removed. ABPA may be identified when the total serum IgE is unusually high but as stated, that is not a discriminating screening tool. ABPA may also be identified in patients with pulmonary infiltrates who undergo lung biopsy and the surgical pathologist makes the diagnosis (56). ABPA may be suspected in the patient initially referred for diagnosis of Allergic Fungal Sinusitis (31, 32).

The differential diagnosis includes conditions that have high peripheral blood eosinophil counts, recurrent pulmonary infiltrates in patients with asthma, elevated total serum IgE concentrations or cause bronchiectasis in patients with asthma. Some conditions to consider are presented in Table 5. Chronic eosinophilic pneumonia in some patients causes the peripheral negative of pulmonary edema meaning peripheral chest roentgenographic and CT infiltrates with blood eosinophilia. This condition responds readily to prednisone but can recur if the prednisone dose is not continued. Acute eosinophilic pneumonia can present as acute respiratory failure with a “white out” chest roentgenogram and no peripheral blood eosinophilia. However, the diagnosis can be suspected when bronchoscopy and bronchoalveolar lavage reveals as much as 60% eosinophils. Churg Strauss Syndrome occurs in patients with asthma who may present with 1) worsening of asthma associated with palpable purpura often on hands or legs, or with 2) onset of a sensory or motor neuropathy. The patient may have poor dorsiflexion of the foot or develop a wrist drop. The third manner of presentation of Churg Strauss Syndrome is with pulmonary infiltrates and peripheral blood eosinophilia that on biopsy demonstrate extravascular granulomas and small vessel (arteries and veins) vasculitis. Some cases appear to occur in the setting of administration of leukotriene D4 antagonists, but whether there is a true cause-effect here is not certain. Patients with acute asthma who have middle lobe syndrome or collapse of upper lobes may have ABPA, but more likely is mucus plugging from status asthmaticus. Treatment with oral or intravenous corticosteroids helps resolve these infiltrates. The total serum IgE concentration can be elevated in such a patient who has asthma and in cases of chronic eosinophilic pneumonia, Churg Strauss Syndrome, parasitism, cystic fibrosis when ABPA has evolved, and in patients with concurrent asthma and atopic dermatitis. The rare patient with Hyper IgE Syndrome can develop ABPA or an overlap condition of ABPA and Hyper IgE Syndrome (17).

When the patient appears to have a bronchopulmonary syndrome but properly performed serologic tests do not support a diagnosis of ABPA, one might explore whether there is another Allergic Bronchopulmonary Mycosis present (43). Culture of sputum or bronchial secretions for fungi may be of value
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and preparation of extracts for in vitro assays from these specimens may be of help to identify the class-specific antibodies. Alternatively, if a patient with asthma and current pulmonary infiltrates, but the skin tests are negative, (most patients with ABPA have many positives as opposed to isolated cutaneous reactivity to A. fumigatus), and the total serum IgE is < 417 kU/L, ABPA or an Allergic Bronchopulmonary Mycosis is excluded.

8. APPROACH TO TREATMENT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

The most effective treatment for ABPA is with prednisone. For over 30 years, antifungal agents have been attempted either by ingestion or inhalation. Most recently, itraconazole was used with apparently more benefit in patients with asthma without bronchiectasis than in patients with bronchiectasis (46). One approach might be to consider antifungals for patients who produce sputum plugs more than once a week and are prednisone dependent (Stage 4). For chronic administration in an attempt to prevent recurrent exacerbations of ABPA, there have been clinical failures with itraconazole and lack of benefit. Patients should determine if their home environment has obvious sources of large amounts of fungi such as basement wall or floor leaks, roof leaks causing damaged dry wall or studs in walls, or repeatedly flooding crawl spaces. These areas should be addressed. Patients should be cautious about shoveling moldy bark and mulch in gardening. Some acute exacerbations of wheezing and ABPA exacerbations have occurred from these activities or exposures. There is no information that allergen vaccine immunotherapy is harmful in ABPA but it is this author’s approach not to include fungi in the vaccine mix. Conversely, some physicians administer allergen vaccine immunotherapy with fungi for patients with Allergic Fungal Sinusitis and believe that this intervention has value. Nevertheless, the patients with Allergic Fungal Sinusitis should receive prednisone initially daily then on alternate days until prednisone can be discontinued along with intranasal corticosteroids and effective surgical interventions. Most patients with ABPA do not required indefinite prednisone administration so physicians should avoid inducing “prednisone-phobia” in patients who must learn to take prednisone at times to prevent new areas of bronchiectasis or pulmonary fibrosis from occurring.

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10. REFERENCES

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43. Greenberger PA: Allergic Bronchopulmonary Aspergillosis in Grammer LC & PA Greenberger eds Patterson’s Allergic Diseases, ed 6, Lippincott Williams & Wilcott, Philadelphia, 2002, 529-554
54. Chauhan B, L Santiago, PS Hutcheson, HJ Schwartz, EA Spitznagel, M Castro, RG Slavin & CJ Bellone: Evidence...
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for the involvement of two different MHC class II regions in susceptibility or protection in allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 2000, 723-729 (2000)


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