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Allergic Bronchopulmonary Aspergillosis: Clinical Manifestations, Diagnosis and Management: Importance of Early Anticipation as One Underlying Cause for Intractable Bronchial Asthma, Cystic Fibrosis Flare Ups

Dr. Liaqat Ali Chaudhry[1], Aftab Ahmed[2]

[1] MRCP, FRCP (Ireland), FCCP (USA), Department of Internal Medicine, King Salman Military Hospital (NWAFH) Tabuk, Saudi Arabia. (Corresponding Author)

[2]Department of Internal Medicine, King Salman Military Hospital Tabuk, Saudi.Arabia.

Running Title: Allergic Bronchopulmonary Aspergillosis

Abstract: ***Allergic bronchopulmonary aspergillosis (ABPA) is a medical condition seen more often in patients having difficult to treat bronchial asthma. It is an immune reaction to the presence of Aspergillus fumigatus present in the airways of patients having bronchial asthma and cystic fibrosis of the lung. The allergic response is archestrated via type-2, T-Helper lymphocytes leading to activation of eosinophilic recruitment and releasing of other inflammatory substances. Manifestations of ABPA include profound cough, breathlessness, wheezing, raised eosinophil counts and total IgE in blood. There are fleeting patchy shadows seen on chest x-rays, which, if not managed early, lead to bronchiectasis. The mainstay of treatment is high dose and prolonged Corticosteroids along with anti-fungal medications. Anticipation of this condition and early management in patients having intractable bronchial asthma help clinical recovery and prevent complications.***

Keywords: Bronchopulmonary Aspergillosis, Bronchial asthma, lung infiltrates

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity pulmonary disease, in reaction to colonization of Aspergillusfumigatus (*A.fumigatus*), which often occurs in those known to have bronchial asthma with a prevalence of 1-2%. Although rates up to 28% are reported in literature with increased frequency in those presenting with intractable asthma. Manifesting as persistent symptoms of cough, wheezing, fever, weight loss, loss of appetite, breathlessness, hemoptysis and abnormal chest x-rays [**1,2,3**].Another lung condition is cystic fibrosis ,associated with increased susceptibility to ABPA, in 7-9% cases (some reports up to 15% cases) observed in relatively younger age group[**4**,**5,6,7**].First time it was described by Hinson and colleagues in 1952.Unfortunately the location of infiltrates or consolidations in ABPA is commonly seen in upper lobes mimicking tuberculosis or as pneumonias not responding to courses of antibiotics and thus delaying the diagnosis. Similarly, symptoms and signs of co-existing ABPA is wheezing and infiltrates, difficult to differentiate from inflammatory hyper-reactive airways of asthmatic patients characterized by wheezing or those having cystic fibrosis and associated with lung infiltrates [**8,9**]. Thus the diagnosis and specific treatment, both are delayed in ABPA until and unless anticipated early.ABPA can also occur in those having atopic conditions like eczema and allergic rhinitis.Therefore ABPA should be suspected in patients having atopic conditions like allergic rhinitis or eczema on presenting first time with respiratory wheeze or having lung infiltrates on chest x-rays mostly without fever and non-responsive to antibiotic courses [**10**,**11**].Rarely association of ABPA has been reported in chronic suppurative lung diseases, congenital immunoglobulin deficiencies, bronchiectasis, and post-lung transplants [**12,13,14,15**].A prevalence of 2-15% of ABPA has been reported in western countries[**16**].

Pathologically ABPA is characterized by excessive mucus plugging the bronchial passages, eosinophilic lung disease or pneumonias resembling histological features of asthma [**17,18]**.There are about 180 species of Aspergillus, but the most common ones affecting human beings are *A.fumigatus*, *A.flavus and A.niger*. *Branching hyphae* of *A. fumigatus* may be seen in the lumen of bronchi filled with mucus in some cases as fungi do not invade the mucosal lining ,however fungus could be seen in about 66 % of ABPA ,on sputum cultures[**19]**.In healthy people immune response orchestrated by neutrophils,alveolar macrophages drawn by cytokines leads to mucocilliary clearing and phagocytosis of fungi spores[**20,21,22]**.If left untreated may lead to fibrotic scarring and bronchiectasis,often in upper zones mimicking tuberculosis[**23,24**].

In people having pre-disposing lung diseases like asthma, cystic fibrosis, rarely chronic granulomatous disease or hyper-IgE syndrome (raised total serum IgE and aspergillus specific IgE), many factors leads to increased incidence of ABPA.These factors include, atopy, and genetic factors like CFTR gene mutations.Both type-I hypersensitivity reaction

(IgE formation) and type-III (IgG) formation are observed.Aspergillusfumigatus antigens and IgE interaction leads to degranulation of mast cells marked with bronchospasm and wheeing.Degranulation of mast cells is further enhanced by Type-2 T helper cells by virtue of their production of interleukin 4 and 5(IL-5), resulting in exacerbation of respiratory symptoms[**25,26,27,28**].Other counter regulatory responses involving IL-6,IL-8 and MCP—1 (a CCL2 recepor ligand) also results in enhanced mast cell degranulation.Proteolytic enzymes secreted by AspergillusintruptIgG function, aimed to destroy the fungus[**29,30**].In one study the molecule OX40 ligand was crucial for driving Th 2 dependant response to fungal antigens in the CD4+ cells of patients of cystic fibrosis and ABPA[**31**].Proteolytic enzymes mediate Th2 cells and IL-8 dependantneutrophilic inflammation [**32**].A small number of patients having ABPA may have con-comitant allergic aspergillusrhinosinusitis[**33,34**]. Many patients are misdiagnosed as tuberculosis in developing countries in 17 to 50% cases, because of lack of awareness and lack of laboratory and radio-imaging facilities[**35**].One other factor is lack of awareness of the general practioners about ABPA.Many patients are thus misdiagnosed as having tuberculosis and are treated with antituberculous drugs sometimes they are given repeated courses.Whereas environment factors and genetic predispositions play a role in the development of ABPA, some HLA-DR molecules like DR2,DR5 and to some extent DR4,DR7 are also associated with increased susceptibility to ABPA[**36,37**].On the contrary HLA-DRQ2 has shown resistance to develop ABPA [**38**]. There are limited studies on the burden of ABPA,it is made more difficult by adoption of non-standardized diagnostic criteria.There are estimates of burden between 0.5-3.5% for ABPA in asthma patients[**39,40**] and 1-17.7% in cystic fibrosis [**41**].In a recent meta-analysis on ABPA complicating asthma,five national cohorts were used based on GINA estimates to assess the burden of ABPA in asthma.Among 193 million asthma patients,ABPA prevalence is estimated to the extremes of 1.35-6.77 million patients.The Eastern Mediterranean region has the lowest estimated prevalence with a predicted case burden of 351,000, while Americans have the highest burden at 1,461,000 cases.These are summed to be underestimates of total prevalence given the exclusion of cystic fibrosis and children below 6 years from the study,and non-availability or limited use of diagnostic laboratory tools in developing regions [**42**].

Diagnosis: Presence of predisposing conditions like bronchial asthma and cystic fibrosis during acute exacerbations and poorly responding to routine bronchodilator and inhaled corticosteroids, including antibiotics should raise the suspicion of allergic bronchopulmonaryaspergillosis.Because early diagnosis and prompt treatment not only results in rapid clinical improvement, but help to prevent complications like parenchymal lung damage leading to lung fibrosis and central bronchiectasis.

Although not validated prospectively one of the following diagnostic criteria has been advocated by the International Society for Human and Animal Mycology(ISHAM) working group for ABPA:

1) Presence of pedisposing conditions (one must be there).
*asthma or
*cystic fibrosis).

2) Obligatory criteria (both must be there)
*Aspergillus skin test positivity or detectable IgE levels against Aspergillusfumigatus.
*elevated total serum IgE,typically>1000IU/Ml,but if the other criteria are present then a level<1000IU/mL may be acceptable.

Other criteria (at least two must be present).
*precipitating antibodies to A.fumigatus.
*radiological lung opacities consistant with ABPA.
* total eosinophil count >500cells/micL in glucocorticoid – naïve patients.

Invasive ABPA occurs in those having an iatrogenic (chemotherapy) or congenital immunodeficiency with neutrophil or macrophage dysfunction and main treatment is with antifungal agents.Aspergilloma or mycetoma is associated with pre-existing lung cavities as seen in treated patients of pulmonary tuberculosis, causing profuse hemoptysis as a complication. Main treatment in such cases is surgery.Hypersenstivity pneumonitis or extrinsic allergic alveolitis is another condition requiring differentil diagnosis from ABPA.It is caused by antigens including bird droppings and feathers causing bird fanciers lung disease,thermophilic moldy hay causing farmers lung,murine urine proteins cause of laboratory worker's lung,aspergillusclavatus moldy brewery barley causing maltworkers lung disease and many others.It is based on immunologic response to various antigens mentioned above via Th 1 cell-mediated reaction with raised titres of specific IgGantibodies.Clinicallyit is characterized by dry cough,fatigue,fever ,anorexia, weight loss and breathlessness. On radio imaging shows micronodularinfiltrates, ground-glass patchy opacities and diffuse patterns.The treatment includes avoidance of exposure to antigens and corticosteroids[**43**].

Diagnosis: There is no consensus on exact criteria for the diagnosis of ABPA, however anticipation based on clinical features in vulnerable patients(asthamatics, cystic fibrosis), supported by abnormal clinical findings(excessive cough, expectoration, fever, breathlessness, hemoptysis) laboratory data (CBC-eosinophilia >500, serology-increased total IgE>417-1000IU/mL and *A.fumigatus* specific IgE and precipitins-IgG on immunoassay, including histopathological features-eosinophilicinfiltrates, broncoconcentricgranulomatosis, mucoid impacted bronchial lumen,central/proximal bronchiectasis,thickening of basement membrane)and radio-imaging (chest x-rays and chest-tomographs),sputum -eosinophils and Charcot-Leyden crystals and may grow fungus on culture and skin testing all help to reach the diagnosis.Peripheraleosinophilic counts are of limited diagnostic value as it could be due to many other causes, like parasitic infestations e.g Loffler's syndrome,and drug reactions etc.Churg Strauss syndrome (eosinophilicgranulomatosis with polyangitis)is a recognized complication in asthmatic patients with peripheral eosinophila,eosinophilic lung disease and total raised IgE associated with allergic broncho pulmonary as per

gillosis.Spirometry may show obstructive or in advanced cases as mixed obstructive and restrictive lung disorder.Some working groups like international society for Human and Animal Mycology,cystic fibrosis foundation, now have proposed specific guidelines on the criteria of diagnosis[**44,45**,**46**].ABPA is rare occurrence in the absence of asthma or cystic fibrosis[**47,48**],however there are published cases in which ABPA occurred without bronchial asthma (Medline research on "allergic bronchopulmonaryaspergillosis") revealed 17 such articles, including a recent case reported in Korea [**49**].

ABPA is classified into following three groups in light of clinical ,serological and radiological findings.[**50**].

1) ABPA-S: Patients have symptoms and signs,supported by laboratory and serological abnormaities excluding bronchiectasis.
2) ABPA-CB: Patients fulfills criteria as mentioned in ABPA-S and has bronchiectasis of central airways.
3) ABPA-CB-ORF: Patients meet diagnostic criteria, has central or proximal bronchiectasis and in addition has advanced irreversible radiological parenchymal lung changes like scarring and hyper-expansion of lungs.

Radiological shadows are seen in 70-80% of patients of ABPA, and include fleeting shadows, due to changing patterns and site, illdefined patchy infiltrates, opacities due to filling of bronchial lumen with mucus and thick exudates are named gloved finger appearance or tooth paste shadows.Dilated bronchiectatic bronchial walls look like tramlines, parallel lines, ring shadows when associated with cystic changes.Gross pathology of ABPA here is cylindrical bronchiectasis of proximal airways particularly of upper lobes [**51,52**].Upto 20-50 percent of these patients are left with residual permanent lung changes on radio-imaging. Among these, 40% cases show peri-hilar shadows mimicking hilarlymphadenopathy.Pleaural effusion is reported in 5% of cases and pneumothorax is a recognized complication.In one study a high resolution tomograph (HRCT-Chest) is shown more sensitive than routine chest-radiographs in about 82% of cases having bronchiectasis, and 64% of those having pleural thickening[**53**].

Greenberger**[54**]standardized the criteria in somebody having(1)asthma,(2)proximal bronchiectasis,(3)immediate cutaneous reaction to antigens of aspergillus species or *A.fumigatus* alone,(4)elevated total IgE>417KU/L or 1000ng/Ml, and (5) raised serum total IgE and/ or raised serum *A.fumigatus* specific IgEs.All of these features may not be present in one case.

Later Patterson etal[**55**] have classified ABPA in to 5 stages.**Stage -I** initial acute phase florid respiratory symptoms characterized by intractable resistant asthma severity, chest radiographic abnormalities and abnormal laboratory data, many patients with ABPA-S (skin test positive) fall in this category.**Stage-II**, the disease goes in remission and lung alveolar shadows clear with falling levels of IgE.**Stage-III**,recurrent exacerbation in asthma symptoms, excessive expectoration, enhanced many fold rise in IgE serum levels.**Stage-IV** is corticosteroid-dependent,patients need continuous corticosteroids on one hand to control their asthma and on the other hand to prevent recurrence of exacerbations.**Stage-V**,is characterized by proximal or central bronchiectasis and fibrosis like irreversible changes(ABPA-CB).

Differentiating ABPA from other common lung diseases remains a challenge in the presence of similar presenting complaints like obstructive airways disease,radiographic findings mimicking atypical pneumonias, associated with raised total IgEs and blood eosinophilia. A high index of suspicion in known asthamatics and atopic individuals narrow the differential diagnosis. Even individuals having no definite history of asthma or central bonchiectsis on CT-Chest, clinicians need to be vigilant for possible seropositive ABPA. Dramatic clinical and radiological response to oral or systemic corticosteroids with or without antifungal agents is another indirect evidence in support of a diagnosis of ABPA.

One single centre study has advocated use of cut-off values of serum IgE (total &*A.fumigatus* specific), eosinophil count in differentiating allergic brochopulmonary aspergillosis from asthma. Diagnosis of ABPA was supported using the best cut-off values of total IgE,*A.fumigatus*IgE and total eosinophils count of 2347IUml,1.91KUA/L and 507 cells/micLrespectively.A combination of these three tests at the mentioned cut-off values provided 100% specificity of differentiating ABPA from asthma[**56**].However, further studies are required at other centres in different geographical regions and ethnic groups.

There are increased sputum eosinophilic cationic protein levels and neutrophil counts in ABPA-CB as compared to allergic bronchopulmonaryaspergillosis-S(ABPA-S).This correlate with severity of bronchiectasis on high resolution chest computrd tomography[**57**].Sputum analysis therefore could be useful in diagnosis as well in monitoring the course of ABPA.

It is difficult to diagnose ABPA in cystic fibrosis as compared to those having bronchial asthma.The Cystic Fibrosis Foundation Consensus Conference recently as proposed following diagnostic criteria especially in CF patients > 6 years of age during clinical deterioration:

1) Acute or sub-acute pulmonary deterioration which is non-attributable to other cause.
2) Total IgE>1000IU/Ml.
3) Immediate reaction to skin testing against A.fumigatus antigen or in vitro specific IgEantibodities to Aspergillus, and
4) One of the following:
   a) Aspergillus serum precipitins.
   b) Elevatedaspergillus specific IgG antibodies. Or
   c) New or recent radiological abnormalities on chest-x-rays or chest tomographs not responding to antbiotics and chest physiotherapy.

Sputum and peripheral blood eosinphila is important in ABPA associated in bronchial asthma but peripheral eosinophila is not marked in Cystic fibrosis and thus is not diagnostically important in patients of cystic fibrosis complicated with ABPA.Skin test used as a screening test for ABPA to aspergillus antigens is positive in 20-30 percent of all asthamatics and 32% in those with ABPA,if negative,

virtually rules out ABPA[**58,59]**.Hemmannetal[**61]**has reported heightened IgE response to recombinant Aspergillus Asp f1,Aspf3,Aspf4,and Aspf6 allergens,while raised IgE levels in response to Asp4 and Aspf6 is said to be highly specific for ABPA in patients of cystic fibrosis. Again it is difficult to differentiate between a bacterial flare and an ABPA in cystic fibrosis, in such situations a useful serum biologic marker is thymus and activation-regulated chemokine(TARC) or CCL17,whose ligand is CCR4 receptor on CD4+ Th2 cells.Latzinetal [**62**]and Hartletal.[**63**] has also reported that TARC was not only elevated in cystic fibrosis with ABPA, but raised further during acute exacerbations of ABPA.

2. Treatment

Underlying conditions need to be managed to prevent exacerbations in the presence of ABPA.This requires control of bronchial asthma and cystic fibrosis including other associated conditions like rhinosinositis [**64**].Mainstay of treatment is corticosteroids in acute phases with rapid relief of symptoms and improved quality of life.Treatment with antifungals twice daily for 4 months,especially with itraconazole is reported definitly beneficial as compared to placebo in double blind randomized controlled trials.Antifungalitraconazole thus has steroid sparing role.Prolonged use of corticosteroids is challenging due to associated immune depression and metabolic derangements (osteoporosis,cushings syndrome, iatrogenic diabetes)and some cases progress to invasive aspergillosis[**65,66,67**].To guard against steroid adverse effects ,doses of corticosteroids are reduced biweekly, anticipating no disease progression after each reduction in dose.Absence of exacerbations for 3months after stopping corticosteroids is considered complete remission.Exception to this assumption is patients who has advanced ABPA,where stopping corticosteroids often results in persisting respiratory symptoms and therefore they are kept on low dose corticosteroids on an alternate-day scedules[**68,69**].Serum IgE can be used to guide treatment along with sputum eosinophil counts at 6-8 weeks of corticosteroid treatment and at interval of 8 weeks for one year.This allows estimation of IgE antibody reference values at a particular time, because in many patients IgE levels don't come down to baseline.High resolution chest tomographs and chest-x-rays are repeated after 4-8weeks of treatment to determine resolution of infiltrates[**70,71**].

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