Allergic Bronchopulmonary Aspergillosis: An Occult Disease Waiting To Be Explored- Case Report And Review Of Literature

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Abstract: Allergic bronchopulmonary aspergillosis (ABPA) is a slowly progressive disease caused by hypersensitivity to *Aspergillus fumigatus*. This condition is most commonly seen in patients with asthma and cystic fibrosis. ABPA mimics a wide range of diseases, thereby further accentuating the difficulties faced by medical practitioners in diagnosing this condition. Even today, this condition remains under diagnosed in many countries with reports of mean diagnostic latency of ten years between the occurrence of symptoms and the diagnosis. We present a case report and review of literature with the aim of highlighting the complicated nature of this enigmatic illness. [Bhatia M NJIRM 2015; 6(6):106-112]

Key Words: Allergic bronchopulmonary aspergillosis (ABPA), Aspergillus fumigatus

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Introduction: Allergic bronchopulmonary aspergillosis (ABPA) is a slowly progressive disease caused by hypersensitivity to *Aspergillus fumigatus*, clinically manifesting as chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis.[1] This condition is most commonly seen in patients with asthma or cystic fibrosis (CF), in whom its prevalence is believed to be approximately 1% and 15% respectively.[1,2] Clinicians are often left clueless about the possibility of development of ABPA in patients as most of them present with symptoms that may be attributed to their underlying disease. Even today, this condition remains under diagnosed in many countries with reports of mean diagnostic latency of ten years between the occurrence of symptoms and the diagnosis.[3] Early diagnosis and treatment has been thought to prevent disease progression, parenchymal damage and loss of lung function. We hereby present a case report and review of literature with the aim of highlighting the complicated nature of this enigmatic illness, which poses a diagnostic challenge for clinicians and laboratory physicians alike.

Case Report: A sixty one years old diabetic male patient presented in outpatient department of a tertiary care hospital in April, 2015 with complaints of significant weight loss, low grade intermittent fever and cough with expectoration since one month. There was no history of dyspnea or chest pain. As per the information given by the patient, he was a non-smoker and known case of chronic asthmatic bronchitis for which he was on medication for over two decades. The patient revealed that he had past history of recurrent attacks of a similar illness during the months of February and March since three years, the details of which are shown in (Table 1). Prior to visiting the hospital, this patient had been under the supervision of a private doctor who subjected him to a wide range of investigations, the results of which were as follows: Hemoglobin:11.1g/cu.mm of blood, hematocrit:34%, total leucocyte count:10,700/cu.mm of blood, polymorphs:75%, lymphocytes:11%, monocytes:6%, eosinophils:8%, basophils: nil, red blood cell count:4.40×10^6/ cu.mm of blood, platelet count:3.06×10^5/cu.mm of blood and erythrocyte sedimentation rate:25mm/hour. Absolute eosinophil count and serum IgE levels were markedly elevated.

Sputum samples of this patient were subjected Gram staining, Ziehl-Neelsen staining (using 3% acid alcohol as decolorizer for acid fast bacilli) and modified Ziehl-Neelsen staining (using 1% sulphuric acid as decolorizer for *Nocardia spp.)* and culture. The sputum was mucopurulent in character and on Gram staining revealed the presence of numerous polymorphonuclear cells, numerous Gram negative bacilli along with normal flora of the upper respiratory tract. No acid fast bacilli or acid fast structures morphologically resembling *Nocardia spp.* were observed on Ziehl-Neelsen or modified Ziehl-Neelsen staining respectively. *Escherichia coli* sensitive to amoxicillin/clavulanate, amikacin, cotrimoxazole, cefotaxime, cefuroxime, ceftriaxone, cefpirome, ofloxacin, levofloxacin, gentamicin, netilmicin, tobramycin, piperacillin-tazobactam, ticarcillin-clavulanate, imipenem, ertapenem, tigecycline and colistin was isolated from sputum sample after twenty four hours of aerobic incubation. Blood culture was sterile after forty eight hours of aerobic incubation.

X-ray chest posterior-anterior view revealed the presence of ill-marginated opacities in right and left perihilar regions respectively, persistent right upper zone opacities, nodular opacity in left perihilar region with prominent bronchovascular markings in both the lung fields (Figure 1). Pulmonary function tests revealed the presence of advanced small airway disease with no significant response evoked by administration of bronchodilator.

The patient was treated with tablet levofloxacin 500 mg twice a day for two weeks, tablet methyl prednisolone 8 mg twice a day for five days, the dose of which was abruptly tapered to 8 mg once a day for the next 5 days subsequently followed by 4 mg once a day for 5 days, inhaler seroflow 250 (containing salmetrol and fluticasone propionate) and tablet paracetamol 500 mg. Although his symptoms resolved completely for a week upon receiving this treatment, however, an X-ray chest which was done subsequently showed persistence and progression of the opacities noted on previous X-ray. It was not long before this patient again developed low grade intermittent fever and cough with mucopurulent expectoration. Sputum sample obtained from this patient was once again subjected to Gram staining and culture. Numerous polymorphonuclear cells, numerous Gram positive budding yeast cells with pseudohyphae, numerous Gram negative bacilli along with normal flora of the upper respiratory tract were seen on Gram stain. *Escherichia coli* sensitive to amoxicillin/clavulanate, amikacin, cefotaxime, gentamicin, tobramycin, piperacillin-clavulanate, imipenem, ertapenem, colistin, levofloxacin (intermediate sensitive) and *Candida spp.* were isolated from sputum sample after 24 hours of aerobic incubation. Owing to these sputum culture results and past treatment history of this patient (as shown in Table 1), tablet fluconazole 150 mg once a week for four weeks was advised in addition to tablet levofloxacin 500 mg twice a day for two more weeks. Methyl prednisolone was discontinued. Although, the patient improved clinically but a chest radiograph done two weeks later revealed radiological deterioration in the form of increase in size of pre-existent opacities along with appearance of a new opacity in left mid zone of lungs.

In lieu of the possibility of a progressive airway disease, the patient decided to seek advice from a senior consultant practicing in a tertiary care hospital where he was advised to undergo multiplanar contrast enhanced high resolution computerized tomography scan of chest. This scan revealed changes suggestive of a chronic and ongoing disease process with features of allergic bronchopulmonary aspergillosis and superimposed infective pathology (Figure 2). In order to gain further clarity regarding the underlying cause, this patient was subjected to bronchoscopy and lavage. Bronchoscopy did not reveal any gross abnormality (Figure 3).

Lavage taken from apical segment of right upper lobe and left lower lobe respectively was subjected to several investigations. Cytopathological examination of bronchial washings showed predominantly polymorphonuclear cells with few groups of columnar cells and alveolar macrophages. Gram stain examination showed numerous polymorphonuclear cells, scanty squamous epithelial cells and no micro organisms. No acid fast bacilli or acid fast structures morphologicaaly resembling *Nocardia spp.* were seen on Ziehl-Neelson and Kinyoun stain examination respectively. Auramine-Rhodamine staining for *Mycobacteria spp.* was negative. No fungal elements were seen on potassium hydroxide mount. Gomori methenamine silver stain revealed the presence of few branching septate hyphae of a fungus morphologically consistent with *Aspergillus spp* (Figure 4). No organisms were isolated from bronchoalveolar lavage specimen after 36 hours of aerobic incubation. No fungus was isolated after four weeks of incubation. Rapid acid fast bacilli culture (BacT/ALERT 3D plus Accuprobe identification without sensitivity) was negative after forty two days of incubation.

Symptoms re-appeared in this patient three days after bronchoscopy. Keeping in mind radiological, cytopathological and preliminary microbiological (microscopy only) findings, a presumptive diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA) was made and treatment with tablet voriconazole 200 mg twice a day for six weeks was started. The patient showed marked clinical and radiological improvement after six weeks (Figure 5). Keeping in mind the chronic character of illness, this patient was advised to continue same treatment for a total period of six months.

Table 1: Table summarizing clinical and treatment history of this patient from 2012 to 2014

YEAR	CLINICAL FEATURES	INVESTIGATIONS PERFORMED				TREATMENT GIVEN	OUTCOME
		SPUTUM CULTURE & SENSITIVITY	CHEST X-RAY	LUNG FUNCTION TESTS	SERUM IgE*		
2012	Low grade intermittent fever & cough with mucopurulent expectoration of >3 weeks duration. History of significant weight loss present.	Not done	Ill marginated opacities in right lung fields with peribronchial cuffing	Results obtained were suggestive of advanced small airway disease	>3000 IU/ml	Tablet betamethasone 1mg once a day (dose tapered gradually) for 4 weeks + Tablet levofloxacin 500 mg twice a day for 2 weeks + Inhaler seroflow 250#	Marked clinical and radiological improvement. Reduction in serum IgE levels to <1500 IU/ml.
2013	Low grade intermittent fever & cough with mucopurulent expectoration of >3 weeks duration. History of significant weight loss present.	*Candida species*	Ill marginated fibrotic opacities in right lung fields with peribronchial cuffing	Results obtained were suggestive of advanced small airway disease	>3000 IU/ml	Tablet betamethasone 1mg once a day (dose tapered gradually) for 4 weeks + Tablet levofloxacin 500 mg twice a day for 2 weeks + Tablet fluconazole 150 mg once a week for 4 weeks + Inhaler seroflow 250	Marked clinical and radiological improvement. Reduction in serum IgE levels to <1500 IU/ml.
2014	Low grade intermittent fever & cough with mucopurulent expectoration of >3 weeks duration. History of significant weight loss present.	*Sphingomonas paucimobilis* sensitive to augmentin, cefuroxime axetil, cefuroxime, ceftriaxone, cefepime, amikacin, ciprofloxacin, ticarcillin-clavulanate and moderately sensitive to levofloxacin	Ill marginated fibrotic opacities in right lung fields with peribronchial cuffing + nodular opacity in left perihilar region	Results obtained were suggestive of advanced small airway disease	>3000 IU/ml	Tablet betamethasone 1mg once a day (dose tapered gradually) for 4 weeks + Tablet levofloxacin 500 mg twice a day for 2 weeks + Tablet fluconazole 150 mg once a week for 4 weeks + Inhaler seroflow 250	Marked clinical and radiological improvement. Reduction in serum IgE levels to <1500 IU/ml.

*Normal serum concentration of IgE is 0-200 IU/ml; IgE stands for Immunoglobulin E and IU stands for International Units. #Inhaler seroflow 250 contains salmetrol and fluticasone propionate.

Figure 1: X-ray chest PA view showing ill-marginated opacities and prominent bronchovascular markings in both the lung fields

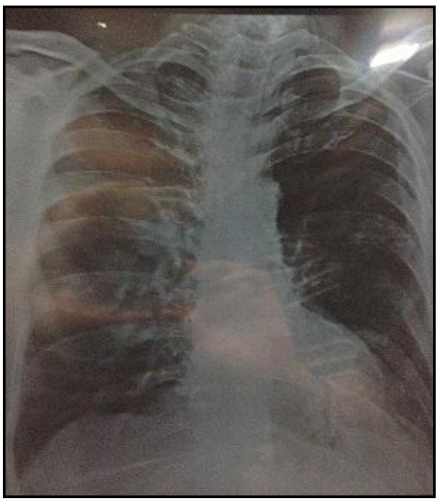


Figure 2: Multi planar CECT showing features of ABPA

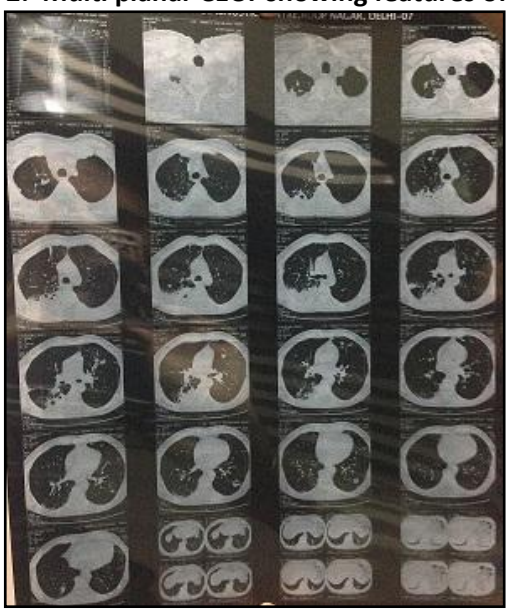


Figure 3: Bronchoscopy showing no gross abnormalities

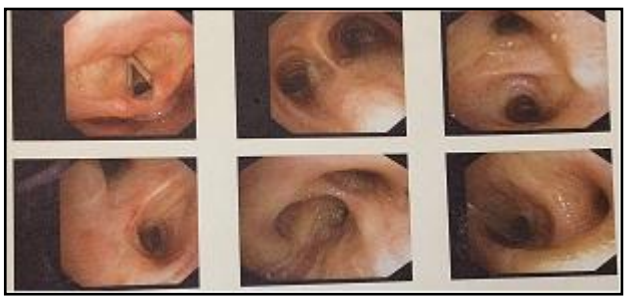


Figure 4: Gomori methenamine silver stain showing branching septate hyphae of a fungus morphologically consistent with *Aspergillus spp*. (400X)

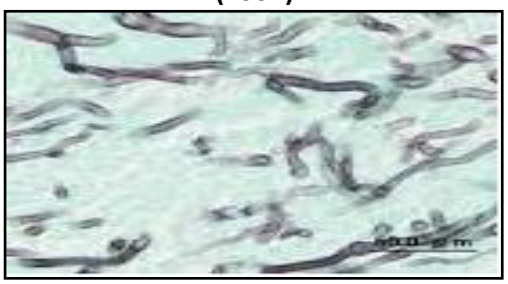
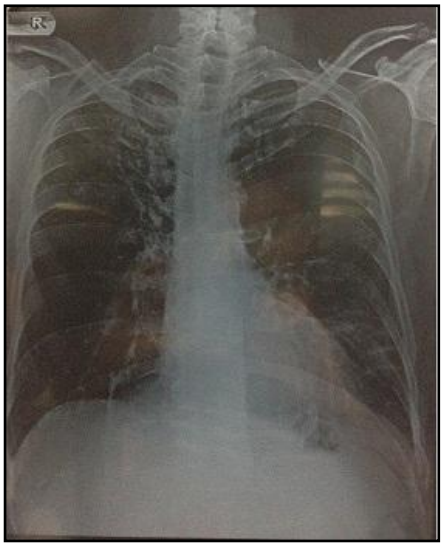


Figure 5: X-ray chest PA view showing marked radiological improvement after six weeks of treatment with voriconazole



Discussion: Allergic bronchopulmonary aspergillosis was first described by Hinson etal in 1952 in the United Kingdom.[4] It is the most frequently recognized presentation of allergic aspergillosis throughout the world. 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.[5] This disease has also been recognized as an upcoming disease in India with prevalence in the range of 7.5% to 27.2%, as reported by different authors.[6,7,8] A number of factors may be responsible for varied reporting of this condition from different parts of the country. There is high prevalence of tuberculosis (TB) in our country and due to striking radiological similarity between ABPA and TB, a large number of ABPA cases may be misdiagnosed as TB and are treated with anti-TB drugs for long periods. Corticosteroids, which are grossly misused in asthmatics in our country, may mask the presentation of ABPA. Further, chest skiagrams are not routinely done in asthma patients in India, thereby, increasing the chances of missing many ABPA cases in the early

stages. By and large, there is lack of awareness about ABPA among physicians. The mycoserological tests and investigations like CT scan required for diagnosing ABPA are not widely available and are rather expensive.[5]

ABPA has immunologic features of immediate hypersensitivity (type I), antigen-antibody complexes (type III), and eosinophil-rich inflammatory cell responses (type IVb), based on the revised Gell and Coombs classification of hypersensitivity reactions.[9] It has very often been observed that despite being exposed to the same environment, all asthmatics do not develop ABPA. This condition is associated with polymorphisms of interleukin (IL) 4Ra, IL-10, SPA2 genes and with heterozygosity of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These associations suggest a strong genetic basis for the development of a TH^2-like allergic response to *Aspergillus fumigatus*.[2] In a genetically predisposed individual, inhaled conidia of *A fumigatus* persist and germinate into hyphae with release of antigens that compromise the mucociliary clearance, stimulate and breach the airway epithelial barrier and activate the innate immunity of the lung.[10] This leads to inflammatory cell influx and a resultant early and late-phase inflammatory reaction.[11]

There are five recognized stages of ABPA, however it does not necessarily evolve through these stages in a sequential manner. New and active ABPA is referred to as stage I. Stage II ABPA is marked by clinical and serological remission. Stage III is recurrent active ABPA. Patients with chronic, steroid-dependent asthma secondary to ABPA are considered to be in stage IV. Fibro-cavitary disease secondary to progressive inflammation and airway dilation is referred to as stage V ABPA, which may lead to progressive respiratory failure and death.[12]

Integration of clinical, serological and radiographic features is required to diagnose this condition. Most patients present with low-grade fever, wheezing, bronchial hyper reactivity, hemoptysis or productive cough. Expectoration of brownish black mucus plugs is seen in 31 to 69% of patients.[6] The differential diagnosis of ABPA includes refractory asthma, newly diagnosed cystic fibrosis, tuberculosis, sarcoidosis, infectious pneumonia, eosinophilic pneumonia, aspergillus sensitive asthma, Churg-Strauss syndrome, bronchocentric granulomatosis and allergic bronchopulmonary mycosis (ABPM) which is a clinical condition identical to ABPA caused by fungi other than *Aspergillus spp*.[13,14] When ABPA is suspected, a serum total IgE level (usually >1000 IU/ml) and skin testing for hypersensitivity to *A. fumigatus* should be performed. A positive skin test in the form of an immediate IgE-mediated response is highly sensitive for *Aspergillus* sensitization but not specific for ABPA.[13] If skin testing is positive and total IgE is elevated, *A.fumigatus* specific antibody levels help to distinguish ABPA from other conditions, such as asthma with sensitivity to *Aspergillus spp*.[13] Serum eosinophilia is not sensitive or specific but if present supports a diagnosis of ABPA.[10] Central bronchiectasis is a hallmark finding, although ABPA without bronchiectasis is also recognized.[15] ABPA-S refers to ABPA diagnosed serologically, whereas ABPA-CB refers to patients with central bronchiectasis. Distinguishing between ABPA-S and ABPA-CB may have prognostic implications as the frequency of exacerbations and the likelihood of permanent lung damage are believed to be lower in patients with ABPA-S.[16]

A number of medications have been tried in the treatment of ABPA. These include systemic and inhaled corticosteroids, antifungal agents and omalizumab, a monoclonal antibody directed against IgE.[13] Systemic corticosteroids are the mainstay of therapy for ABPA. These are associated with decreased wheezing, serum total IgE levels and eosinophilia and resolution of parenchymal opacities.[17] However, corticosteroids do not inhibit the growth of *Aspergillus spp*.[18] To decrease the burden of fungi and prevent continued antigenic stimulation and subsequent inflammation, antifungal therapies such as nystatin, amphotericin B, natamycin, and ketoconazole have been tried.[13] Ketoconazole showed some benefit but was associated with significant side effects. Itraconazole has been used with greater success and tolerability.[19] Rai et al from India have shown encouraging results with itraconazole and fluconazole although, fluconazole has no activity against *Aspergillus spp.*[20,21] Current recommendations are to consider antifungal drugs as a corticosteroid sparing agents or if corticosteroids alone are ineffective.[13] Voriconazole, a newer antifungal azole with greater bioavailability, has the potential to be more effective, with case reports attesting to its benefit.[22] Case reports of improvement with omalizumab suggest that anti-IgE therapy may be of benefit.[23]

The patient under study had clinical, serological and radiological features suggestive of ABPA. However, fungal elements suggestive of *Aspergillus spp.* were visualized only by Gomori methenamine silver stain examination of BAL fluid. Although, direct microscopic examination using 10-40% potassium hydroxide or Gram stain may be extremely valuable in diagnosing fungal infections, one must keep in mind that both false positive and negative results may occur. When present in small numbers, special stains such as Gomori methenamine silver and Periodic acid Schiff are essential for detecting and characterizing the morphology of *Aspergillus spp.* in clinical samples.[24] Fungal culture of BAL fluid was negative even after four weeks of incubation. The diagnostic utility of culture varies widely with the fungal species, the specimen source and the disease state of any given fungal infection. In many clinical instances, fungal culture techniques are often too slow or have reduced yield to be relied on as the sole laboratory modalities for the diagnosis of endemic and opportunistic fungal infections.[25] Sputum or broncho alveolar lavage culture may be falsely positive (as *Aspergillus spp* are not only commonly encountered as laboratory contaminants but also, colonizers of airways in some patients) or falsely negative in patients with ABPA.[2]

This patient had experienced recurrent episodes of acute exacerbations of his symptoms every year with new opacities appearing in chest radiographs, indicating reactivation of local inflammatory process after discontinuation of treatment. Although, treatment with systemic and inhalational steroids, levofloxacin and fluconazole led to clinical improvement in the preceding years, this patient eventually responded to treatment with voriconazole. Fluconazole is often prescribed by pulmonologists to control and eradicate *Candida spp.* colonization of airways. *Candida spp.* was isolated from two different sputum samples obtained from this patient on different occasions. In lieu of the possibility of colonization of respiratory tract of this patient with *Candida spp.,* fluconazole was prescribed. However, the refractoriness of this patient to treatment given in the preceding years can be explained by the fact that exposure to fluconazole probably led to the development of drug resistant strains of *Candida spp.* and *Aspergillus spp.* respectively. Similar observations were made by Foula V et al in a diagnosed case of mixed allergic bronchopulmonary aspergillosis and candidiasis wherein, exposure to fluconazole therapy eventually led to repeated isolation of drug resistant strains of *Aspergillus niger* from sputum samples of this patient.[26]

Fortunately in the present case, timely intervention helped us to correctly diagnose this condition which led to initiation of appropriate therapy and continued clinical and radiological improvement.

Conclusion: This case report cum review of literature clearly highlights the fact that the diagnosis of ABPA is a daunting task. ABPA mimics a wide range of diseases, thereby further accentuating the difficulties faced by medical practitioners in diagnosing this condition. An integrated approach consisting of clinical, radiological and microbiological inputs is required for timely diagnosis and effective management of this condition.

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