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Allergic Bronchopulmonary Asper Gillosis : An Update

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Abstract :

Allergic bronchopulmonary asper gillosis (ABPA) is an immunologically mediated lung disease which occurs predominantly in patients with asthma, and is caused by hypersensitivity to colonized Aspergillus fumigatus. It is a chronic, relapsing disorder which can clinically range from mild asthma to fibrotic lung disease. The immunopathogenesis of the disease is not clearly understood. Early diagnosis and aggressive therapy with oral corticosteroids can prevent the development of fibrotic lung disease and are, therefore, the cornerstone of management.

***Key Words** : ABPA, update*

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Introduction :

The spectrum of Aspergillus-associated respiratory disorder ranges from saprophytic colonization of the respiratory tract to rapidly invasive disseminated disease. For clarity sake, it can be broadly clasified into three clinical categories, viz. allergic aspergillosis, aspergilloma and invasive aspergillosis, (Table I).

Allergic bronchopulmonary aspergillosis (ABPA), the most frequently recognised manifestation of aspergillosis, occurs worldwide[1]. It is an immunologically mediated jung disease which usually occurs in atopic individuals and is caused by hypersensitivity to the antigen of the fungus Aspergillus especially A. fumigatus. Although ABPA is predominantly a disease of the asthmatics, only a very few .asthmatics actually suffer from it. Furthermore, inspite of familial preponderance of asthma, familial occurrence of ABPA is a rarity[2]. The explanation for this still remains a subject of speculation. The exact prevalence of disease is not known but contemporary western estimates suggest that ABPA complicates 1-6% of all chronic cases of asthma. Allergic Aspergillus sinusitis (AAS) is a more recently recognised; clinical entity in which mucoid impaction similar to that of ABPA occurs in the paranasal sinuses[3].

Table-I

Aspergillus associated respiratory disorders

I.	Allergic aspergillosis.
	Allergic bronchopulmonary aspergillosis (ABPA)
	IgE mediated asthma
	Hypersensitivity pneumonitis
	Allergic Aspergillus sinusitis (AAS)
II.	Saprophytic colonization
	Aspergilloma
III.	Invasive disease
	Invasive disseminated aspergillosis
	Chronic necrotizing pneumonia.

The Organism

The fungus. Aspergillus derives its name from its resemblance to brush used for sprinkling holy water called aspergillum. The main pathogenic species are A. fumigatus (accounts for about 95% of Aspergillus-related illness in humans), A. flavus, A. niger, A. terreus and A. nidulans. The fungi exist only in mycelial form and are thermotolerant,

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capable of growing at temperatures between 15-53°C, the optimum being 37-40°C.

These ubiquitous organisms can be easily isolated from growing or stored vegetation, decaying organic matter, fallen leaves, soil or air. The spores are dispersed by wind in the atmosphere. thus, inhalation is the primary route of infection for most cases of all forms of aspergillosis. Spore counts show seasonal variations, higher counts associated with increase in the exacerbation of ABPA[4].

Diagnostic Criteria

The diagnostic criteria[5,6] of ABPA are summarised in Table-II. A series of diagnostic criteria is required as apart from demonstration of central bronchiectasis (CB) there is no individual test, which establishes the diagnosis or is not affected by therapy with oral prednisolone. The presence of central/proximal bronchiectasis in the absence of distal bronchiectasis is considered a sine qua non for the diagnosis of ABPA and when present, the patient can be categorised as ABPA-CB. However, CB may also extend to the periphery in a small number of segments[7]. It is now recognised that a group of patients presenting at an earlier stage of the disease or with milder form of the disease may not have CB. Such seropositive patients who satisfy all the criteria for ABPA except CB can be categorised as ABPA-S, and treatment commenced to prevent further lung damage.

Table-II

Diagnostic criteria for ABPA

Major criteria
asthma
presence of radiologic infiltrates
immediate cutaneous reactivity to A. fumigatus
elevated total serum IgE
precipitating antibodies against A. fumigatus
peripheral blood eosinophilia
elevated serum IgE and IgG to A. fumigatus
central/proximal bronchiectasis with normal tapering of distal bronchi
Minor criteria
expectoration of golden brownish sputum plugs
positive sputum culture for Aspergillus species
late (Arthus-type skin reactivity to A. fumigatus

Clinical Features

An indolent disease with a protracted course, clinically ABPA can range from mild asthma to fatal destructive lung disease. It is characterized by repeated episodes of exacerbation interspersed with periods of remission, culminating if untreated in fibrotic lung disease, which resembles the chronic fibrocavitary disease of pulmonary tuberculosis. Although it can occur at any age, the patient is usually in the 20-40 years age-group and often presents with poorly controlled asthma and peripheral eosinophilia. The symptoms may also be due to pulmonary consolidation and the patient may present with cough, purulent sputum, wheezing, dyspnoea, fever and malaise, chest pain and even haemoptysis. Expectoration of golden brownish sputum plugs is not uncommon and should raise the possibility of AMAPA[8]. Patients with chronic fibrotic disease may present with cyanosis and respiratory failure. However, symptoms appear to bear little or no relationship to severity orchronicity of the disease, as a third of the patients may be relatively asymptomatic inspite of extensive radiological lesions. Allergic bronchopulmonary'aspergillosis may also be associated with other clinical allergic diseases in the form of rhinitis, conjunctivitis, skin and food allergies.

With rare exceptions, the clinical catetgories of Aspergillus related respiratory disorders usually remain mutually exclusive. Co-existent ABPA with aspergilloma, though infrequent, has been reported[9,10,11], but inspite of similar immunopathologic responses, concomitant occurrence of ABPA and AAS is a rarity[12], while association of ABPA, AAS and aspergilloma in a single patient has been document, only once[13]. Syndromes similar to ABPA caused by fungal species other than Aspergillus also occur, but appear to be rare. Collectively, they are known as allergic bronchopulmonary funguses (ABPF).

Physical examination in ABPA may be completely unremarkable in the asymptomatic patient or it may reveal rhonchi, crackles and bronchial breathing depending on the degree of lung disease present. If extensive fibrosis has resulted from ABPA, crackles may be heard in affected areas,

which do not clear after tussive effort or after treatment with oral corticosteroids. Some patients with end features of corpulmonale. Associated hypertophic osteoarthropathy has also been reported[10].

Radiology

Radiological changes[14,15,16] may be transient or permanent (Table-III). The former may be the result of mucoid impaction, secretions in the damaged bronchi and parenchymal infiltrates, these may clear with or without therapy with corticosteroids. Chest radiological changes, most commonly seen in the upper lobes, can closely resemble those seen in tuberculosis, but serial radiographs in ABPA may reveal transient nature of pulmonary infiltrates, also know as fleeting shadows[13]. The patient may also present with lobar or segmental collapse. Ipsilateral pelural effusion with collapse in a case of ABPA has also been reported[13]. Of the permanent changes, the most important one is central/proximal bronchiectasis with normal peripheral bronchi, a pathognomonic feature of ABPA. While presenting the CT appearances in 23 patients with ABPA, we identified CB in all patients involving 85% of the lobes and 52% of the segments studied. Central bronchiectasis extended to the periphery in 34% of these lobes and at the segmental level, peripheral to the periphery in 34% of these lobes and at the segmental level, peripheral broncliiectasis was identified in 21 % of the segments[7]. It is believed that bronchiectasis occurs in areas with previous radiological lesions which may result in fibrosis[9]. Demonstration of CB is considered a sine qua non for the diagnosis of the diseases for which bronchography was regarded as a gold standard. However, computed tomography (CT) of the thorax is now accepted as an effective alternative in the diagnosis of bronchiectasis. We have shown that CT in comparison to bronchography, a procedure thought to be unsafe in asthma, has a sensitivity of 83% and a specificity of 92% in dectecting CB in patients with ABPA and could thus be the investigation of choice[17]. Computed tomograms also enabled us to rapidly and safely establish the diagnosis in children with ABPA who presented with acute severe asthma[18]. Bronchiectasis on CT is characterized by 'string of pearl' and 'signet ring' appearances as described by Webb et al[19]. Although cavitation is not a common feature of ABPA, it can occur along with the fibrotic stage of ABPA[16] when it may be difficult to distinguish from fibrocavitary pulmonary tuberculosis[10,11,20]. Interestingly, CT scans revealed pleural involvement in 43% of the patients, a feature yet to be highlighted. However, it may not be of major clinical significance[7]. Computed tomography of the thorax provides a sensitive method for assessment of bronchial, parenchymal and pleural abnormalities in cases of ABPA and should constitute a part of the initial work up of the disease[7].

Laboratory Findings

Immediate cutaneous reactivity to Aspergillus antigens is invariably positive but is also positive in 25% of asthmatic without ABPA[21] A delayed Arthus type reaction can also be seen. Peripheral blood eosinophilia is not uncommon and during exacerbation most patients have an absolute eosinophil count between 1000 to 3000 per cumm, unless the patient is already on therapy with prednisolone. In a patient who has a productive cough, sputum eosinophilia is often present and sputum culture may yield Aspergillus species in about 58% cases[8].

Serological tests are valuable in the diagnosis of ABPA. Precipitating antibodies against A. fumigatus, as demonstrated by double immunodiffusion technique of Quchterlony, can be detected in 90% of patients with a radiological infiltrate but may require serum to be concentrated five-folds[8]. Precipitating antibodies may also be present in 10% of asthmatics who do not have. ABPA[21]. Total serum IgE levels are generally greater than 1000 IU/ml and may be as high as 20,000 IU/ml in acute cases except in cases who are in remission or on therapy with prednisolone. It is a useful monitor of therapy as a fall of 35% in eight weeks is suggestive of effective therapy while doubling of remission values indicates an exacerbation in an asymptomatic patient[3].

Table-III

Radiological changes in ABPA

Transient changes
Perihilar infiltrates simulating adenopathy.
Air-fluid levels from dilated central bronchi filled with fluid and debris
Massive consolidation-unilateral or bilateral
Radiologic infiltrates
'toothpaste' shadows due to mucoid impactions in damaged bronchi
'gloved finger' shadows from distally occluded bronchi filled with secretions
'tramline' shadows representing oedma of the bronchial walls
Collapse - lobar or segmental
Permanent changes
central bronchiectasis with normal peripheral bronchi
Parallel-line shadows representing bronchial widening
Ring-shadows 1-2 cm in diameter representing, dilated bronchi en face
Pulmonary fibrosis
Late changes-cavitation contracted upper lobes and localized emphysema

A difficult diagnostic problem in ABPA is to differentiate a patient ABPA from a patient with asthma and immediate cutaneous reaction to Aspergillus. This can be done by comparing serum IgG and IgE antibody activity against A. fumigatus (IgG-Af and IgE-Af) in both groups of patients. In ABPA, double the serum values of IgG-Af and IgE-Af are found as compared to asthmatic with a positive immediate cutaneous reaction to Aspergillus. In an appropriate clinical setting, the high serum levels of IgG-Af or IgE-Af can be diagnostic of AMAPA[3,6].

Pulmonary Function Testing

Pulmonary function testing in ABPA is relatively insensitive and does not help to define the extent of disease or exclude it. Patient in remission can have normal lung Volumes and flow rates if the asthma is well-controlled even in the presence of bronchiectasis. During an acute episode, pulmonary function testing may show a seduction in total lung capacity (TLC), vital capacity (VC), forced expiratory volume in frst second (FEV1) and impaired diffusion capacity for carbon-monixide (Dlco) but return to baseline after therapy with prednisolone. Patients with fibrotic lung disease typically have reduced lung volumes, low diffusion capacity and irreversible airflow obstruction[22].

Pathologic Findings

Pathological changes[14] include dilated bronchi containing tenacious mucus and fibrin as well as changes characteristic of asthma such as Curschmann's spirals, Charcot Leyden crystals within the lumen and airway inflammation with eosinophils and mononuclear cells. Fungal hyphae may be seen in the bronchial lumen but do not invade the bronchial wall or parenchyma. Cellular infiltrates, especially activated eosinophils, are present which is indicative of an inflammatory-reaction rather than an immune complex mediated mechanism at the site of bronchial wall destruction[23].

Immunopathogenesis

As mentioned earlier, it is still not known as to why some patients with asthma develop ABPA. The immune mediated mechanisms of lung destruction are largely unknown. It is thought that viscid sputum present in susceptible asthmatics traps A. fumigatus spores permitting the thermotolerant fungus to colonise the airways, injure the bronchial epithelium and permit absorption of the A: fumigatus antigens. This evokes a polyclonal antibody response[17] leading to elevated total IgE and A. fumigatus specific IgE, IgG and IgA antibodies indicating a humoral and cellular TH2- immunoligic response. This strong humoral and cellular response points towards an immuno-competent and activated defense system against the pathogenic fungi. A glycoprotein antigen with an apparent molecular weight of 45 kD predominant in the circulating immune complexes was recently isolated from patients with ABPA. It appears that there are two major components involved (1) chronic exposure to A. fumigatus and (2) an exaggerated host response involving cytokine release[27] lymphocyte sensitization and complement activation, which could result in lung damage. A recent report has shown that lung surfactant proteins A and D can inhibit the ability of allergic-specific IgE from patients with ABPA and may thus be involved in the modulation of allergic sensitization and/or

development of allergic reactions in these patients[28].

Treatment

The goals of treatment of ABPA are (1) to detect and treat ABPA exacerbations promptly so as to prevent or minimize bronchiectasis that develops at the site of infiltrates; (2) manage associated asthma irreversible lung disease; (3) exclude ABPA in family members, and (4) identify a potential environmental source of the incriminated fungus.

Oral corticosteroids are most effective and remain the cornerstone for the treatment of ABPA. For stages I (acute) and III (exacerbation), prednisonone is given 0.5mg/kg/day as a single morning dose for two weeks and then converted to an perhaps monthly for the first year, is a valuable monitor as total serum IgE declines by at least 35% within two months of initiating prednisolone therapy and is associated with resolution of the acute infiltrate on chest radiology.

After three months of alternate-day prednisolone, therapy and reduction of total serum IgE to a baseline concentration (the baseline total serum IgE can remain elevated despite clinical and radiological improvement), prednisolone can be tapered off. Stage IV ABPA patients are managed with prednisolone, usually on alternateday dose of 10-40mg for several years as repeated attempts to discontinue it may result in unacceptable wheezing. If prednisolonel can' be discontinued, the patient should be evaluated monthly or every 6 weeks initially to help determine whether remission (stage II) is maintained or whether the patient goes into stage III or IV. Stage V patients may require daily prednisolone, and when marked lung destruction occurs, they require continuous therapy for corpulmonale and arterial hypoxaemia.

Many other agents such as antifungal agents, cromolyn sodium and inhaled steroids have been tried but have not proved to be beneficial. Anti-asthma therapy may be needed for control of asthma but they do not prevent exacerbation of ABPA.

Conclusion :

In conclusion, a high index of suspicion is required to establish a diagnosis of ABPA which should excluded in patients with history of increasing severity of asthma, a positive -immediate cutaneous reactivity to A. fumigatus, history of recurrent pneumonitis, transient pulmonary infiltrates and bronchiectasis. In our country, mycoserological investigations are not widely available while radiological investigations like bronchography and CT scan are not easily done. This results in diagnostic delay and increased morbidity. Furthermore, the remarkable radiological similarity to pulmonary tuberculosis has important clinical implications as patients with ABPA often receive anti-tuberculous therapy for a long time while lung damage continues to progress silently. Early diagnosis and appropriate therapy could alter the progress of the disease and prevent the development of end-stage lung fibrosis.

References :

1. Shah A. Allergic bronchopulmonary aspergillosis: An emerging disease in India (editorial). Indian J Chest Dis Allied Sd 1994; 36: 169-172.
2. Shah A. Khan ZU. Chaturvedi S. Bazaz Malik G, Randhawa HS: Concomitant allergic Aspergillus sinusitis and allergic bronchopulmonary aspergillosis associated with familial occurrence of allergic bronchopulmonary aspergillosis Ann Allergy 1990; 64.: 507-512.
3. Greenberger PA. Allergic bronchopulmonary aspergillosis In: Middleton E (Jr), Reed CE. Ellis EF. Franklin AN (Jr.), Yunginger JW, Busse WW ed. Allergy: Principles and Practice; 4th ed. St. Louis: CV Mosby Co; 1993; 1395-1414.
4. Shah A. Khan ZU, Sircar M, Chaturvedi S. Bazaz Malik G, Randhawa HS. Allergic Aspergillus sinusitis : An Indian report.' Respir Med 1990; 84 : 249-251.
5. Rosenberg M. Patterson R. Mintzer R. Cooper BJ. Roberts M. Harris KE.Clinical and immunological criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Arm Intern Med 1977; 86: 405-414.
6. Wang JLF. Patterson R, Rosenberg M, Roberts M, Cooper BJ. Serum IgE and IgG antibody activity against Aspergillus fumigatus as a diagnostic aid in allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1978; 117: 91792.

7. Panchal N, Bhagat R, Pant C, Shah A. Allergic bronchopulmonary aspergillosis : The spectrum of computed tomography appearances. Respir Med 1997; 91: 213-219.

8. Mccarthy OS, Pepys J. Allergic bronchopulmonary aspergillosis: Clinica immunolog and clinical features. Clin Allergy 1971; 1 : 261-286.

9. Safirstein BH, D'Souza MF, Simon G, Tai EHC.,Pepys J. Five year follow up of bronchopulmonary aspergillosis. Am Rev Respir Dis 1973; 108 : 450-459.

10. Shah A, Khan ZU. Chaturvedi S. Ramachandran S,Randhawa HS, Jaggi OP. Allergic bronchopulmonar aspergillosis with, co-existent aspergilloma. A long term follow up. J Asthma 1989; 26 : 109-115.

11. Agarwal AK, Bhagat R, Panchal N. Shah A. Allergic bronchopulmonary aspergillosis with aspergilloma mimicking fibrocavitary pulmonary tuberculosis. Asian Pacific J Allergy Immunol 1996; 14 : 5-8.

12. Shah A, Bhagat R, Panchal N, Jaggi OP. Khan ZU. Allergic bronchopulmonary aspergillosis with middle lobe syndrome and allergic Aspergillus sinusitis. Eur Respir J 1993; 6 : 917-918.

13. Bhagat R, Shah A, Jaggi OP, Khan ZU. Concomitant allergic bronchopulmonary aspergillosis and allergic Aspergillus sinusitis with an operated aspergilloma. J Allergy Clin iminunol 1993; 91: 1094-1096.

14. Mc'Carthy DS. Simon G, Hargreave FE. The radiological appearances in allergic bronchopulmonary aspergillosis. Clin Radiol 1970; 21 : 366-375.

15. Mintzer RA, Rogers LF, Kruglik GD. The spectrum of radiological findings in allergic bronchopulmonary aspergillosis. Radiology 1978; 127 : 301-307.

16. Phelan MS. Kerr IH. Allergic bronchopulmonary aspergillosis: The radiological appearance during long term follow up. Clin Radil! 1984; 35 : 385-392.

17. Panchal N. Pant CS. Bhagat R. Shah A. Central bronchiectasis in allergic bronchopulmonary aspergillosis : Comparative evaluation of computed tomography of the thorax with bronchography. Eur RespirJ 1994; 7 : 1290-1293.

18. Shah A. Pant; CS, Bhagat, R. Panchal N. CT in childhood allergic bronchopulmonary aspergillosis. Pediacr Radiol 1992; 22 : 227-228.

19. Webb WR. Muller NL, Naidich OP. ed. High-resolution CT of the Lung; 2nd ed New York: Lippincott - Raven Publishers. 1996; 257-258.

20. Shah A. Bhagat R. Panchal N. Childhood allergic bronchopulmonary aspergillosis with clubbing and cavitation. Indian Pediatr 1993; 30 : 248-25 1.

21. Schwartz HJ. Atron KM. Chester EH. et al. A comparison of sensitization to Aspergillus antigens among asthmatics in Cleveland and London. J Allergy Clin Immunol 1978; 62 : 8-14.

22. Nichok D. DoPico GA. Braun S. Imbeari S. Peters ME. Rankin J. Acute and chronic pulmonary function changes in - allergic bronchopulmonary aspergillosis. Air. J Med 1979; 67 : 631-637.

23. Slavin RG, Bedrossian CW, Hutcheson PS et al. A pathological study of allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 1988; 81 : 718-725.

24. Bhatnagar PK, Banerjee B, Shah A, Sarma PU. Probable role of IgG subclasses in patients with allergic bronchopulmonary aspergillosis. Serodiogn Immunother Infec Dis 1993; 5 : 123-124.

25. Kauffman HF, Tomee JFC, Vander Werf TS, DeMonchy JGR, Koeter GK. Review of fungus induced asthmatic reactions. Am J Respir Crit Care Med 1995; 151 : 2109-2116.

26. Madan T, Banerjee B, Bhatnagar PK, Shah A, Sarma PU. Identification of 45 kD antigen in immune complexes of patients of allergic bronchopulmonary aspergillosis. Mole Cell Biochem 1997; 166 : 111-116.

27. Bhatnagar PK, Banerjee B, Shah A, Sarma PU. Circulating complement (C3), C3 and