

PATHOLOGY OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Anne Chetty

Department of Pediatrics, Floating Hospital for Children, New England Medical Center, Boston, MA

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1. ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with asthma and cystic fibrosis when *Aspergillus fumigatus* spores are inhaled and grow in bronchial mucus as hyphae. Chronic colonization of *Aspergillus fumigatus* and host's genetically determined immunological response lead to ABPA. In most cases, lung biopsy is not necessary because the diagnosis is made on clinical, serologic, and roentgenographic findings. Some patients who have had lung biopsies or partial resections for atelectasis or infiltrates will have histologic diagnoses. A number of different histologic diagnoses can be found even in the same patient. In the early stages the bronchial wall is infiltrated with mononuclear cells and eosinophils. Mucoid impaction and eosinophilic pneumonia are seen subsequently. This may be followed by bronchiolitis obliterans, granulomatous bronchiolitis, and pulmonary fibrosis. Treatment with corticosteroids appears to prevent the progression of the disease.

2. INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an immune bronchial disease occurring in children and adults with chronic lung diseases such as bronchial asthma and cystic fibrosis. This pulmonary disorder arises from an allergic response to multiple antigens expressed by *Aspergillus fumigatus* (Af). Pulmonary infiltrates, eosinophilia and sputum production are characteristic. Other forms of lung diseases such as invasive aspergillosis occurring in immunocompromised individuals and aspergillomas, that occurs in preexisting lung cavities, should be distinguished from IgE mediated Af hypersensitivity. *Aspergillus* is found in decaying vegetation, soil especially in humid climates. In temperate climates *Aspergillus* is one of the common indoor allergens responsible for asthma and ABPA. Swimming pools, basements that are moist and humid for prolonged periods of time harbor these fungi. ABPA may develop in

individuals with episodic obstructive lung diseases such as asthma and cystic fibrosis that produce thick, tenacious sputum.

Decomposing organic matter serves as a substrate for the growth of *Aspergillus* species. Because biologic heating produces temperatures as high as 65° to 70° C, *Aspergillus* spores will not be recovered in the latter stages of composting. *Aspergillus* species have been recovered from potting soil, mulches, decaying vegetation, and sewage treatment facilities, as well as in outdoor air and *Aspergillus* spores grow in excreta from birds (1)

Allergic fungal pulmonary disease is manifested in six different forms namely, invasive aspergillosis, aspergilloma, IgE mediated allergic asthma and sinusitis, hypersensitivity pneumonitis, chronic necrotizing pneumonia and ABPA. Invasive form of aspergillosis occurs in immunocompromised individuals. The spores or conidia of the organism 3 micron in size reaches the bronchi via inhalation, invades the pulmonary parenchyma and tracheobronchial tree and extend into the blood vessels disseminating into other organs via blood stream (2).

In ABPA, the *Aspergillus* organism colonizes in the respiratory tract in patients with asthma and cystic fibrosis. Colonization induces immune response to multiple antigens of Af. *Aspergillus flavus*, *Candida*, *Penicillium*, *Curvularia* and *Dreschleria* are also implicated in the pathogenesis of ABPA (3). Currently ABPA is diagnosed more frequently than in the past. ABPA is present in 2% of patients of asthma in the community setting and 28% of patients with asthma in the referral Setting (4).

Clinical findings are described elsewhere in this issue. Briefly, ABPA can occur at any age, developing in individuals with atopy. Patients have recurrent episodes of asthma exacerbation with wheezing and chest infiltrates.

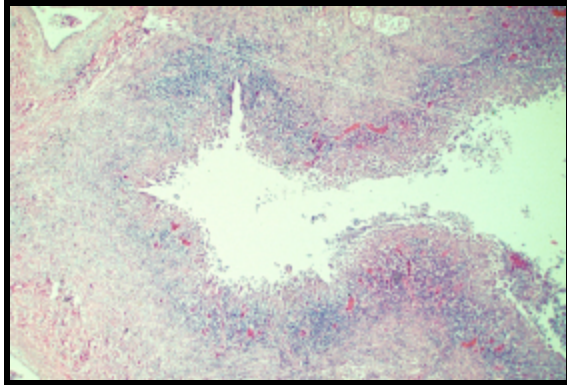


Figure 1. Bronchocentric granulomatosis. The walls of the small bronchus is replaced by granulomatous inflammation (courtesy of E. Mark, M.D, MGH, Boston, MA).

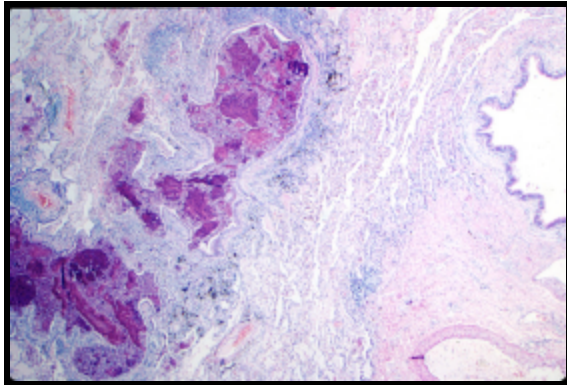


Figure 2. Bronchocentric granulomatosis. The lumen of the bronchioles are filled by impacted mucus. The lung is scarred (Courtesy of E. Mark, M.D, MGH, Boston, MA.).

They have systemic manifestations such as fever, malaise and anorexia. Sputum production is characterized by chunks of green to beige colored sputum plugs (5). Mucus plugging results in partial obstruction of airways leading to bronchiectasis as a complication.

3. IMMUNOPATHOGENESIS

Aspergillus fumigatus organism colonization occurs in the respiratory tract or sinuses of atopic individuals leading to the production of several antigens. Colonization of the respiratory tract with Af leads to the production of over 20 antigens and the resultant hypersensitivity reactions are both IgE mediated (type I) and IgG mediated (type III) (6). When *Aspergillus* begins to grow in the bronchial tree, it causes IgE production, either by direct stimulation of B cells capable of producing IgE or indirectly by activation of T cells. The specific IgE and IgG antibodies combine with some of the *Aspergillus* antigen generated in airway secretions resulting in immune complex formation. This causes damage to the bronchial walls and initiates eosinophilic infiltration into the lung (7). Eosinophils release mediators, such as eosinophil cationic

protein, major basic protein, and peroxidase. These mediators can cause direct tissue damage and may contribute to bronchoconstriction. Cell-mediated component to the hypersensitivity reaction leads to granuloma formation and mononuclear cell infiltration in the lungs of patients with ABPA (8;9). Th1 cells preferentially secrete IFN gamma and are responsible for cell-mediated immunity reactions, cytotoxic lymphocytes, and provide help for IgG2a production. Th2 CD4+ cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13; provide help for immunoglobulin (particularly IgE and IgG₄ in humans and IgE and IgG₁ in mice) secretion; enhance eosinophil production, survival, and activity; and promote mast cell proliferation and maturation.

Computed tomography (CT) findings in allergic bronchopulmonary aspergillosis consist primarily of mucoid impaction and bronchiectasis involving predominantly the segmental and subsegmental bronchi of the upper lobes. *Aspergillus* necrotizing bronchitis may manifest as an endobronchial mass, or collapse, or a hilar mass. Bronchiolitis is characterized by branching linear or nodular areas of increased attenuation (10).

4. PATHOLOGIC FINDINGS

In most cases, lung biopsy is not necessary because the diagnosis is made on clinical, serologic, and roentgenographic findings. Some patients who have had lung biopsies or partial resections for atelectasis or infiltrates will have histologic diagnoses. A number of different histologic diagnoses can be found even in the same patient. In the early stages, mucoid impaction and eosinophilic pneumonia are seen. This may be followed by bronchiolitis obliterans, granulomatous bronchiolitis, and pulmonary fibrosis (11) (12). Lipid pneumonia, vasculitis, bronchocentric granulomatosis, and neutrophil-eosinophil exudative bronchiolitis have also been described on lung biopsy specimens or at postmortem examinations. In the largest case series of surgical specimens from patients with ABPA, Bosken et al characterized the pathology associated with ABPA (12). Surgery was performed for diagnosis of recurrent or persistent pulmonary infiltrates. All cases showed bronchocentric granulomatosis or mucoid impaction of bronchi, or both.

The main abnormalities of ABPA are the inflammatory reaction involving bronchi and bronchioles. In bronchocentric granulomatosis there is replacement of bronchial wall by granulomatous inflammation. A transition from bronchiolar epithelium to granulomatous inflammation is seen commonly (Figure 1).

When the epithelium is completely replaced the lesion resembles a granuloma. This granulomatous lesion consists of histiocytes surrounded by lymphocytes and plasma cells. Eosinophils are also present in the infiltrate. The center of the lesion contains necrotic tissue and granular eosinophilic material (Figure 2). Fungal hyphae can be seen in the necrotic material. In some cases vasculitis can be noted in adjacent vascular structures due to chronic inflammatory cell infiltration.

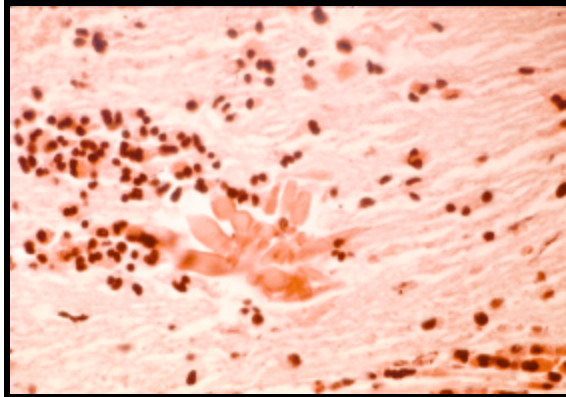


Figure 3. Charcot-Leyden Crystals. The speculated eosinophilic crystals lie within the mucus adjacent to eosinophils. (courtesy of E. Mark, M.D, MGH, Boston, MA).

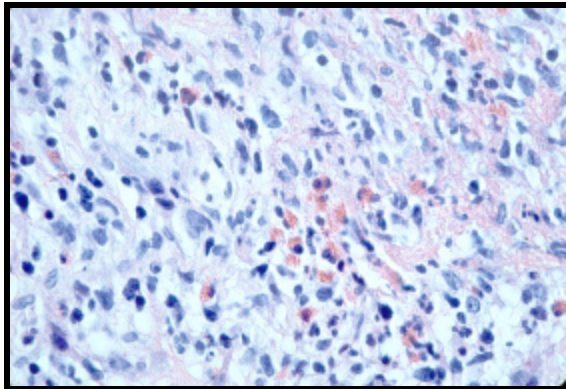


Figure 4. Eosinophilic Pneumonia. Alveoli filled with histiocytes (blue) and groups of eosinophils (pink) (courtesy of E. Mark, M.D, MGH, Boston, MA).

Mucoid impaction is seen in almost all cases of ABPA. The involved bronchi are usually dilated and contain mucoid material consisting of necrotic eosinophils, epithelial cells, and amorphous debris. *Aspergillus* hyphae may be identified but they rarely invade the bronchial wall⁽¹³⁾. Inflammation of bronchial wall is associated with mononuclear cells and eosinophils infiltration. Bronchial wall destruction occurs with collagen replacing submucosal glands and muscle fibers (14). It is not uncommon to see bronchocentric granulomatosis or mucoid impaction during a lung biopsy for a mass like infiltrate to rule out cancer or from bronchoscopic biopsy for an obstructing bronchial mucus plug (15). In ABPA "allergic mucin" is often present. it is characterized by fibrin, Curschmann spirals, Charcot-Leyden crystals, and eosinophils. Fungal hyphae may be difficult to identify, as they do not present as branching, septate structures but rather as end-on cross-sections of the hyphae that resemble gram-positive cocci. Charcot-Leyden crystals are seen in this material. They appear as refractile pink needles in longitudinal section or hexagons in cross section (Figure 3).

Exudative bronchiolitis seen in these patients are probably secondary to mucoid impaction or

bronchocentric granulomatosis. Bronchiolar lumen contains similar necrotic material consisting of breakdown products of eosinophils and other inflammatory cells. Fragmented fungal hyphae may also be present in the bronchioles. Chronic bronchiolitis, another common finding is characterized by infiltration of bronchiolar walls with inflammatory cells consisting of lymphocytes, plasma cells and eosinophils. As the disease progresses a foreign body giant cell reaction to necrotic material will be seen in the adjacent areas of the affected bronchi and bronchioles. Bronchiolitis obliterans and organizing pneumonia are seen in late stages. In bronchiolitis obliterans the lumen is occluded by organizing fibrous tissue with proliferating capillaries in the center.

Eosinophilic pneumonia is usually seen in the distal lung parenchyma and the lesion is very focal, characterized by accumulation of eosinophils and macrophages within the alveolar spaces. Similar cells infiltrate alveolar walls. During a resection of superior segment of left upper lobe for a cavitary and infiltrative lesion Imbeau et al found collapsed alveoli containing large mononuclear cells, few lymphocytes, plasma cells, and clumps of eosinophils (11). There is interstitial accumulation of histiocytes, lymphocytes and eosinophils (Figure 4).

It is important to mention here that both bronchiolitis obliterans and eosinophilic granuloma share the causative factors and clinical features of hypersensitivity reaction to *Aspergillus* organisms, drugs, aspiration pneumonia, and collagen vascular disease.

ABPA should be differentiated from other types of aspergillosis namely saprophytic aspergillosis (SPA) and invasive aspergillosis. Hebisawa et al examined 38 surgical specimens of SPA (16). SPA cavities had macroscopic ulcers (81.6%) and bronchi originating from the cavities (68.4%). Microscopically, SPA cavities showed shallow ulcers (100%), coagulation necrosis (42.1%) and granulomatous reaction (52.6%). In invasive aspergillosis coagulation necrosis, fungal balls in cavitary lesions and suppurative lesions were found. In allergic bronchopulmonary aspergillosis hard or firm mucous plugs were found in the proximal bronchi, peripheral to this bronchocentric granulomatosis with tissue eosinophilia was noted. Fungal hyphae were recognized in both mucous plugs and peripheral lesions.

Mucoid impaction has been described in other conditions including chronic bronchitis and cystic fibrosis. In these conditions without ABPA, the necrotic material consists of epithelial cells and neutrophils. The necrotic material in the bronchi in ABPA consists of eosinophils and Charcot-Leyden crystals in addition to the other inflammatory cells.

The fungal hyphae in the impacted mucus in the bronchi and bronchioles may mimic aspergillomas. Aspergillomas are fungal balls found within lung cavities and they are packed with fungal hyphae that may be mixed with necrotic material (Figure 5).

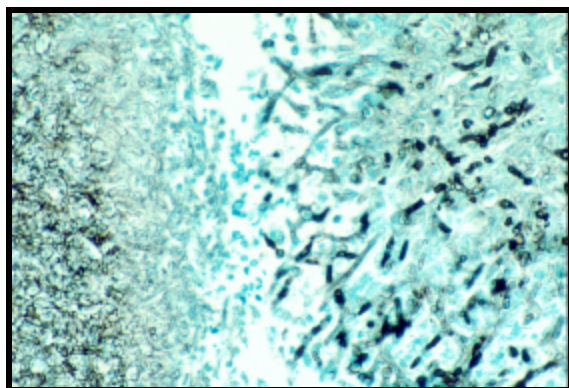


Figure 5. Aspergilloma. *Aspergillus* stained with Silver stain representing aspergilloma (left) and hyphae of invading *Aspergillus* (right) (courtesy of E. Mark, M.D, MGH, Boston, MA).

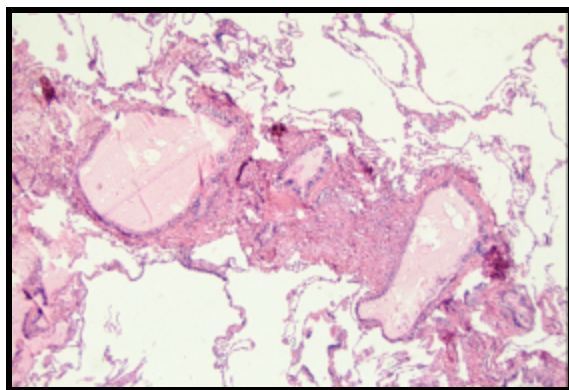


Figure 6. Mucus plugging in a patient with plastic bronchitis: Bronchiole filled with mucus plug, a white gelatinous material (courtesy of E. Mark, M.D, MGH, Boston, MA).

4.1. Plastic bronchitis

Plastic bronchitis is a rare disorder characterized by the formation and expectoration of branching bronchial casts. Disorders associated with plastic bronchitis are allergic bronchopulmonary aspergillosis, asthma, cystic fibrosis, pneumonia, and chronic bronchitis; and in conditions where there are obstructions or structural abnormalities that decrease mucous clearance, such as bronchiectasis or congenital heart disease. Bronchofibroscopy reveals diffuse tracheobronchitis with casts occluding the bronchi. X-ray shows alveolar infiltrate and high resolution CT scan shows ground glass opacity. Microscopic examination of the lung from an adult patient with ABPA and plastic bronchitis shows Whitish thick gelatinous material filling the lumen of the bronchus is seen (Figure 6).

4.2. Allergic fungal sinusitis

This was first described by Katzenstein et al (17). They described seven cases of paranasal sinusitis in which the pathological findings were similar to ABPA. These patients had a history of asthma, nasal polyposis, mucoid impaction of the bronchi and chronic sinusitis. The airway secretions are usually slimy and contain degenerating

eosinophils, Charcot-Leyden crystals and cellular debris. Fungal elements may be seen and cultures may be positive. Since the initial report, several cases of sinusitis with ABPA have been recognized including a case of sinopulmonary syndrome with the history of sinus disease, bronchiectasis and pulmonary nodules recently described in an adult patient who had allergic fungal sinusitis associated with ABPA (18)

4.3. ABPA in cystic fibrosis

ABPA was reported in two children with cystic fibrosis in 1965 (19). The reported prevalence of ABPA in CF is as high as 15% (20) (21). Discrepancies in the reported prevalence rate are due to lack of accepted diagnostic criteria and under recognition of the disease in CF population.

Familial occurrence of ABPA has been reported, suggesting a possible genetic contribution to the disease (22) (23). This possibility is further suggested by the development of ABPA-like features in a substantial proportion of patients with cystic fibrosis (CF). CFTR gene mutations, in combination with environmental or other genetic factors, could be involved in the pathogenesis of ABPA in patients (24). The possibility that CFTR could play a role in the pathogenesis of ABPA is also supported by the finding of a high frequency of the [DELTA] F508 mutation in ABPA patients with bronchiectasis (25). Heterozygosity for CFTR mutations could either predispose to the development of bronchiectasis with secondary sensitization to Af or promote immune response to Af, leading to airway inflammation and bronchiectasis. The bronchiectatic airways in cystic fibrosis patients are suitable for colonization by Af organisms. *Aspergillus* organisms are commonly found in the respiratory secretions of adult CF patients. Treatment to eradicate the fungus is unnecessary, as tissue invasion has rarely been reported to occur. As many as 10% of the adult CF population will experience bronchospasm secondary to allergic bronchopulmonary aspergillosis (26), (27). Isolation of *Aspergillus* from the respiratory tract following lung transplantation is common and generally not associated with tissue-invasive disease. Those CF recipients with *Aspergillus* isolated in cultures of sputum preoperatively are at increased risk for postoperative infections with this agent (28).

5. ACKNOWLEDGEMENT

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Send correspondence to: Anne Chetty, M.D., Department of Pediatrics, New England Medical Center, 750 Washington Street, Boston, MA 02111, Tel: 617-636-8739, Fax: 617-636-4233, E-mail: achetty@lifespan.org