

Review article

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) occurs in nonimmunocompromised patients and belongs to the hypersensitivity disorders induced by *Aspergillus*. Genetic factors and activation of bronchial epithelial cells in asthma or cystic fibrosis are responsible for the development of a CD₄ + Th2 lymphocyte activation and IgE, IgG and IgA-AF antibodies production. The diagnosis of ABPA is based on the presence of a combination of clinical, biological and radiological criteria. The severity of the disease is related to corticosteroid-dependant asthma or/and diffuse bronchiectasis with fibrosis. The treatment is based on oral corticosteroids for 6–8 weeks at acute phase or exacerbation and itraconazole is now recommended and validated at a dose of 200 mg/day for a duration of 16 weeks.

I. Tillie-Leblond*, A.-B. Tonnel*

Department of Pulmonology and Immuno-Allergology, University Hospital of Lille, Lille, France

*Present address: Unité INSERM U416, Institut Pasteur, and Department of Lung Disease and of Immuno-Allergology, Lille, France

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André-Bernard Tonnel
Department of Pulmonology and Immuno-Allergology
A. Calmette Hospital
1, rue Leclercq
CHRU
59037 Lille Cedex
France

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Aspergillus organisms are extremely resilient and ubiquitous in the environment. Although the pathophysiology of the various pulmonary manifestations related to *Aspergillus* infection remains complex and poorly understood, the severity of these conditions seems to depend mainly on the quantity and virulence of the inhaled *Aspergillus* inhaled and on the status of the host defence. Clinical, biological, pathological and radiological features differ depending on the type of disease: saprophytic infestation, invasive diseases or allergic diseases such as hypersensitivity pneumonitis, *Aspergillus*-mediated asthma and allergic bronchopulmonary aspergillosis (ABPA). The ABPA occurs in nonimmunocompromised patients, in the absence of invasive aspergillosis, and is defined as a hypersensitivity disorder induced by an *Aspergillus* species. The activities of polymorphonuclear leucocytes and alveolar macrophages, cell types involved in host defence against *Aspergillus*, are not impaired in patients with ABPA. Most patients with ABPA have either asthma or cystic fibrosis. The inhalation of spores from the environment is followed by growth of hyphae in the mucus of the bronchial tree and stimulates an immune response involving Th2 CD4 + T-cells and IgE and IgG antibodies. This disease was first reported in 1890 and was later described by Hinson et al. in 1952 (1) in 12 asthmatics with recurrent pulmonary infiltrates, eosinophilia (blood and sputum) and *Aspergillus* hyphae in their sputum.

Precipitating antibodies to *Aspergillus* were identified by Pepys in 1969 (2).

Aspergillus

Aspergillus fumigatus is involved in the majority of ABPA cases. However, clinical and radiological features similar to those observed in *A. fumigatus* ABPA cases are occasionally seen in association with other fungi (such as *Stemphylium lanuginosum*, *Helminthosporium* species, *Candida* species, *Curvularia* species, *Schizophyllum commune*, *Dreschlera hawaiiensis*, *Fusarium vasinfectum*) and other species of *Aspergillus* (*A. niger*, *A. flavus*, *A. nidulans*, *A. orizae* or *A. glaucis*) (3–5). This review focuses on *A. fumigatus*, the *Aspergillus* species that most frequently infects humans. In the mycelium phase, *Aspergillus* exists in the form of 7–10-µm long, septate, uniform hyphae with dichotomous branching at an angle of 45°. The hyphae can be identified using the PAS and Grocott's stains. Reproduction is characterized by the formation of conidiophores with terminal vesicles producing chains of spores. The spores measure between 2 and 4 µm in diameter, are thermotolerant (grow at temperatures ranging from 15 to 53°C) and are able to grow on Sabouraud dextrose agar slants (6). Conidiophores and spores may be seen together, mainly in structures that are

in contact with the atmosphere. *Aspergillus* is ubiquitous in the environment, existing in water, decaying organic materials, soil spaces, wood chips, mown vegetation, basements/indoor air, walls or ceilings, particularly when these environments contain moisture. *Aspergillus*-related diseases are most common in individuals working in the farming industry, where it is recognized as an occupational disease. Identification of *Aspergillus* in cultures derived from the sputum of individuals with ABPA does not necessarily mean that the fungus is implicated in the disease. A relationship between the level of exposure to *Aspergillus* and the occurrence of ABPA has not been clearly identified, although Radin et al. (7) suggested that high levels of exposure are associated with ABPA exacerbations. Inhalation of conidia is followed by airway colonization. In some individuals, proliferation of the fungus in the airway lumen results in chronic bronchial inflammation and an IgE-mediated hypersensitivity response, blood eosinophilia and production of local and blood precipitating antibodies (8–11). *Aspergillus* spores also bind to activated epithelial cells and basement membrane components. Epithelium activation occurs in individuals with asthma and in those with cystic fibrosis, and may facilitate *Aspergillus* penetration of the bronchial mucosa. A positive correlation has been identified between impaired pulmonary function and the presence of serum antibodies to *A. fumigatus* in cystic fibrosis patients.

Pathophysiology

The factors underlying the development of ABPA remain unclear. The roles of genetic factors, mucus quality, preactivation of epithelial cells and the extent to which this activation facilitates the development of *Aspergillus* spores into hyphae, bronchial penetration of *Aspergillus*, the immune response and bronchial/bronchiolar inflammation and destruction are not yet fully understood. Indeed, the mechanisms involved in ABPA development are complex (Fig. 1). Pepys suggests that ABPA is a result of types I and III immunologic responses, classified according to Gell and Coombs. However, this classification provides a restricted view of ABPA pathogenesis.

Genetic factors

The CD4+Th2 lymphocytes from ABPA patients are restricted to six MHC class II HLA-DQ subtypes. Genetic studies suggest that HLA-DR molecules (DR2, DR5, and possibly, DR4 or DR7) are associated with susceptibility to ABPA, whereas HLA-DQ2 molecules are associated with resistance. Thus, a combination of these genetic elements may determine the outcome of ABPA in patients with cystic fibrosis and asthma (12, 13). Marchand et al. (14) found that the frequency of cystic fibrosis transmembrane conductor regulator (CFTR) gene mutations was high in patients with ABPA compared to those with

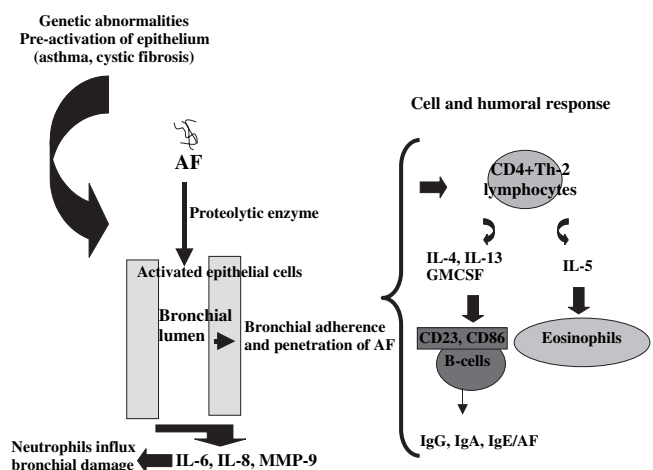


Figure 1. Pathophysiology of ABPA. From *Aspergillus* adherence and penetration of the bronchial mucosa to the B and T cell response.

allergic asthma, even though both groups showed normal sweat chloride concentrations. This indicates that CFTR gene mutations are involved in the development of ABPA. In addition, Saxena et al. identified an association between polymorphisms in the collagen region of pulmonary surfactant protein-A2 and a predisposition to ABPA and severity of the disease (15).

The conditions under which *A. fumigatus* colonizes the respiratory tract in patients developing ABPA is another factor associated with the pathophysiology of the disease. *Aspergillus* spores are inhaled and penetrate the mucus layer. A combination of factors may lead to greater bronchial adherence of *Aspergillus* and high levels of *Aspergillus* antigen absorption in patients developing ABPA: proteolytic enzymes secreted by *Aspergillus* (16), epithelial cell activation in individuals with asthma or cystic fibrosis and impaired mucus clearance in cystic fibrosis cases (17). Indeed, *A. fumigatus* activates epithelial cells, resulting in the secretion of increased amounts of IL-6 and IL-8 and up-regulation of epithelial cell detachment (18). This activation process is partly dependent on the Protease Activated Receptor 2 (19). ABPA occurs in only a low percentage of *Aspergillus* skin test-positive asthmatic individuals (20). Thus, *Aspergillus* skin test-positive asthmatic individuals must be clearly differentiated from ABPA patients, as sensitivity to *Aspergillus* is not sufficient to diagnose ABPA. These patients may also be sensitized to other fungal spores (*Cladosporium*, *Alternaria*, *Stemphylium*, etc.).

Aspergillus antigens strongly activate both T and B cells (12, 21–25). Lymphocyte activation has been shown in humans and animal models. CD4+Th2 lymphocyte activation is thought to be involved in ABPA. The number of GM-CSF, IL-4 and IL-5 positive cells was higher in ABPA murine models than in controls (26) and IL-10 seemed to be a natural suppressor of pro-inflammatory cytokine production (27). Schuyler (28)

demonstrated that interleukins stimulate IgE and IgG synthesis, mast cell proliferation, and eosinophil activation and survival. IL-4 is involved in IgE production and eosinophil activation via the up-regulation of VLA-4 and CCR-3 expression (29–31). Elevated blood sIL-2 receptor concentrations and higher levels of CD23 expression on B-cells were found in ABPA patients than in patients with asthma but no ABPA (32). The increase in CD23 expression is also partly mediated by IL-4 (29). The T-cell response in ABPA patients was associated with *B-cell activation* and the presence of IgE, IgA and IgG in the blood and bronchial cells. Divergent results have been obtained from studies of blood and bronchoalveolar lavage (BAL) secretion of immunoglobulins directed against *A. fumigatus*. These inconsistencies may be explained by differences in the detection methods used: some authors have evaluated precipitating antibodies, whereas others have used ELISA or RIA methods. Moreover, the quality of the antigen extracts differed considerably between studies. The use of recombinant antigens should improve detection rates and make the results of these studies more reproducible and reliable. The IgE response is largely, but not exclusively, directed towards *A. fumigatus* epitopes (9). Total serum IgE production is thus nonspecific and probably enhanced by the local production of large amounts of IL-4. The levels of IgE-*Aspergillus*-specific antibodies were higher in the BAL than in the blood (33). The same was true of IgA-AF antibody production. In contrast, no differences between BAL and blood secretions have been reported for IgG-*A. fumigatus* antibodies (33). This suggests that the IgE and IgA antibodies to *A. fumigatus* are synthesized locally.

Tissue damage (bronchiectasis formation) occurs in ABPA patients as a consequence of the local influx of neutrophils and eosinophils. Sputum eosinophil and neutrophil levels are higher in ABPA patients with bronchiectasis than those without bronchial destruction (34). The extent of the bronchiectasis, detected by high resolution CT-scan, correlates with the eosinophil and neutrophil sputum counts but not with total IgE levels in the serum (34). Recently, Gibson et al. demonstrated that IL-8 gene expression and protein levels in the sputum were higher in ABPA patients than in controls and that the extent of this alteration correlated with the degree of bronchial neutrophilia and airway obstruction (35). Thus, IL8 may be a key mediator of tissue damage in ABPA.

Pathology of ABPA

Pathologic specimens are not necessary for diagnosis. In cases where bronchial samples have been taken, the bronchial tree was dilated and filled with mucus plugs containing macrophages, eosinophils, Charcot–Leyden crystals and sometimes hyphae or hyphal fragments (36, 37). Bronchial walls were infiltrated with inflammatory

cells (eosinophils, lymphocytes and plasma cells), and a thickening of the basement membrane and epithelial abrasion were also found (38). The pathology of the peribronchial areas and parenchyma may differ from that described above: bronchocentric granulomatosis with bronchial remodelling and dilation have been described (39). However, bronchocentric granulomatosis is a distinct entity often associated with a pseudo-tumoral radiologic pattern (38), and possibly with other conditions such as tuberculosis, inflammatory diseases of the bowel and rheumatoid arthritis (40–43). The infiltration of the parenchyma with mononuclear cells, eosinophils and lymphocytes leads to inflammation that mimics or is associated with the patterns observed in individuals with other forms of interstitial disease such as granulomatous bronchiolitis, exsudative bronchiolitis or obliterans bronchiolitis (38). Microabscesses with *Aspergillus* hyphae and granulocytes have been described in the parenchyma, demonstrating that the frontier between invasive and allergic diseases is sometimes poorly delimited.

Diagnosis of ABPA

ABPA occurs mainly in asthmatics and patients with cystic fibrosis.

In asthmatic patients, the diagnosis of ABPA is based on the presence of a combination of clinical, biological and radiological criteria. The prevalence of ABPA is difficult to establish. When screening was performed in patients with persistent asthma, the prevalence was between 1 and 2%. (20, 44). The major criteria are listed in Table 1. Eight criteria for ABPA diagnosis were initially identified, but only some of them are essential. The nonessential criteria, for example, pulmonary infiltrates or blood eosinophilia may be only present at the time of exacerbation or during the acute phase of the disease.

Bronchiectasis, involving the more central segmental bronchi is a strong diagnosis criterion but is not always present in patients during follow-up and at the time of diagnosis. Greenberger et al. (45) identified two bases for differentiating ABPA patients with and without bronchiectasis: ABPA with central bronchiectasis and seropositive ABPA without bronchiectasis. When a patient with asthma does not have bronchiectasis the following criteria are sufficient for ABPA diagnosis: high total serum IgE levels associated with an immediate cutaneous reaction to

Table 1. Criteria for the diagnosis of ABPA (patients without cystic fibrosis)

Asthma
Immediate cutaneous reaction to <i>A. fumigatus</i>
Total serum IgE concentration (>1000 ng/ml)
Elevated <i>A. fumigatus</i> -specific serum IgE levels
Precipitating antibodies to <i>A. fumigatus</i> in the serum
Peripheral blood eosinophilia (not essential for diagnosis)
Chest Roentgenographic infiltrates (not essential for diagnosis)
Central bronchiectasis

Aspergillus, elevated *Aspergillus*-specific IgE (or IgG) levels and the presence of precipitating *Aspergillus* antibodies in the serum. In other cases, particularly in the absence of systemic corticosteroids, elevated blood eosinophil counts, marked increases in precipitating *Aspergillus* antibodies or pulmonary infiltrate allow ABPA diagnosis (46). Several other criteria are also taken into consideration: mucoid impactions have been described in 14–54% of ABPA patients (37, 47) and *Aspergillus* has been found in the sputum, particularly in the plugs, in some cases (2, 37).

In cystic fibrosis patients, ABPA is a common complication of this disease, occurring in approximately 10% of cases. Diagnosis of ABPA in cystic fibrosis patients is difficult for several reasons. Several of the criteria used for ABPA diagnosis are common manifestations of cystic fibrosis. Cystic fibrosis patients often present exacerbations with bronchial obstruction, pulmonary infiltrate and bronchiectasis (48, 49). In addition, cystic fibrosis patients may have immune responses to *Aspergillus* (IgE, IgA, IgG antibody production and elevated total serum IgE levels), in the absence of ABPA. The boundary separating these responses from those involved with ABPA is difficult to define (50–52). Recently, the Cystic Fibrosis Foundation has proposed a new set of criteria for ABPA diagnosis in cystic fibrosis patients (53):

- clinical deterioration (coughing, wheezing, increased sputum production, exercise intolerance and decrease in pulmonary function);
- immediate hypersensitivity to *A. fumigatus* (positive skin test or IgE response);
- total serum IgE concentration > 1000 kUI/l;
- precipitating antibodies to *A. fumigatus*;
- abnormal chest roentgenogram (infiltrate, mucus plugs or unexplained changes compared to previous chest X-ray).

These criteria are particularly valuable for diagnosis in cases where the condition of the patient has only slightly improved, or not improved at all, after treatment for bacterial bronchial infection. The recommendation is that cystic fibrosis patients should be screened for ABPA from 6 years of age, once a year or in response to clinical suggestions of ABPA.

The Epidemiologic Register of Cystic Fibrosis reported that ABPA prevalence was 7.8% in 2000 (ranging from 2.1% in Sweden to 13.6% in Belgium). The prevalence of ABPA was low in patients who were less than 6-year old. ABPA was more common in patients in a poorer clinical condition [lower Forced Expiratory Volume in 1 s (FEV1), higher rate of microbial colonization, poor nutritional status]. Most of these patients had a delta f508/delta f508 genotype (54). Due to this strong association between cystic fibrosis and ABPA, it may be useful to perform sudoral tests on patients showing signs of ABPA. In some patients cystic fibrosis was diagnosed at the same time as ABPA (55).

In other conditions, although rare, cases of ABPA have been reported in patients without asthma (56–58). The ABPA has been described in patients with other chronic obstructive pulmonary diseases and in association with allergic fungal sinusitis, bronchocentric granulomatosis, hyper-IgE syndrome (Buckley) and chronic granulomatous disease. In the case of these neutrophil disorders, differentiating between ABPA and an invasive disease related to *Aspergillus* is sometimes difficult. When ABPA is diagnosed, invasive aspergillosis can be fatal in patients with hyper-IgE syndrome or chronic granulomatous disease as, systemic corticosteroids may accelerate tissue damage and invasive fungal infections.

Clinical characteristics and stages of ABPA

The ABPA onset can occur in childhood (59) but is more frequent in young adults. Most patients have other allergic disorders, such as rhinitis, conjunctivitis, atopic dermatitis and sensitization to common pneumallergens and trophallergens. The ABPA onset occurs at the time of, or more frequently after, asthma onset and is usually associated with the transformation of mild asthma into corticosteroid-dependent asthma, with unusual symptoms such as malaise, fever (body temperatures reaching 38.5°C), presence of sputum plugs and purulent sputum, coughing or increased coughing, chest pains and hemoptysis (60). Pulmonary consolidation without bacterial infection has been observed. Physical examination does not give any useful information. In patients with consolidation or fibrosis, crackles may be heard on breathing. In cystic fibrosis patients, exacerbation may be associated with weight loss and a marked increase in productive coughing.

ABPA progresses in *five stages* (61); listed in Table 2.

Treatment differs depending on the ABPA stage. Patients with acute exacerbation respond to corticosteroids and early treatment of pulmonary infiltrate with these drugs can prevent bronchial or bronchiolar destruction. Long-term treatment with corticosteroids is not recommended because this treatment does not prevent the emergence of new infiltrates, or progression to fibrosis. Measuring total serum IgE levels is helpful for monitoring the treatment regimen (Table 2). Total serum IgE levels are high during the acute or exacerbation phases of ABPA, levels then decrease slowly over a mean period of 6 weeks. By the end-stage, prognosis and treatment resemble those for cystic fibrosis patient management: of these patients have extensive bronchial destruction and the bronchial tree may be colonized by *Staphylococcus aureus* and/or *Pseudomonas aeruginosa*. Response to corticosteroids is limited at this stage. However, progression from stage I to V is not inevitable and progression from stage IV to V is particularly uncommon.

Kumar (62) studied the characteristics of ABPA patients and found that individuals with the disease could be divided into three groups: ABPA with positive

Table 2. Stages of ABPA (according to Patterson et al.)

Stages	Clinical characteristics	Biology	Radiology
I: acute	Fever, cough, chest pain, hemoptysis, sputum	Elevated total serum IgE +++ levels (±blood eosinophilia)	Pulmonary infiltrate(s) (upper/middle lobes)
II: remission	Asymptomatic/stable asthma	Normal or elevated total serum IgE +levels	No infiltrates (in the absence of systemic corticosteroid therapy for >6 months)
III: exacerbation	Symptoms mimicking the acute stage or asymptomatic	Elevated total serum IgE +++ levels (±blood eosinophilia)	Pulmonary infiltrate(s) (upper/middle lobes)
IV: cortico-dependent asthma	Persistent severe asthma	Normal or elevated total serum IgE + levels	With or without pulmonary infiltrate(s)
V: Fibrosis (end-stage)	Cyanosis, severe dyspnea	Normal or elevated total serum IgE + levels	Cavitary lesions, extensive bronchiectasis, fibrosis

serology (ABPA-S), ABPA with central bronchiectasis (ABPA-CB) and ABPA with central bronchiectasis and other radiologic features (ABPA-CB-ORF). Pulmonary function abnormalities were mild in the ABPA-S group, moderate in the ABPA-CB group and severe in the ABPA-CB-ORF group. Absolute eosinophil counts raised in each groups but were highest (1.233/ml) for the ABPA-CB-ORF group. The levels of *A. fumigatus*-specific IgE followed the same pattern, with a maximum of 47.91 UI/ml for the ABPA-CB-ORF group. Symptom scores were also higher for the ABPA-CB-ORF group than for the other groups. Thus, the ABPA-S group probably contained patients with early stage or a less aggressive form of ABPA. The studies of Greenberger et al. (45) and Greenberger (63) lead them to suggest that early recognition and treatment of ABPA may prevent progression to end-stage ABPA.

Biology

Nearly all ABPA patients show an *immediate cutaneous reaction* to skin pricks with an *Aspergillus* mixture. The dual reaction is rare, about 16–33% of patients. (64, 65). Patients may also have sputum and/or blood *eosinophilia*, particularly at the time of diagnosis or when exacerbations occur at times when they are not receiving corticosteroids. In these situations, blood eosinophil levels may be unusually high, between 1500 and 3000/mm³ (47). *Aspergillus* can be detected in the *sputum* of 50% of ABPA patients (47). The most reliable diagnostic tests are measurements of total serum IgE and serum IgE and IgG AF antibody levels and determination of the presence AF antibody precipitins (results are expressed as the number of precipitation lines). Some *Aspergillus* antigens (catalase, trypsin and chymotrypsin) are essential for these reactions. These enzyme activities can be detected after gel diffusion and, as these antigens appear to be specific to AF, may be useful for diagnosis (66). Variation of level of specific antibodies are function of treatment, age and stage of ABPA (67–69). Total serum IgE levels are high in ABPA patients, and decrease when they are in remission

as a result of corticosteroid treatment. This decrease usually occurs within 2 months after initiation of corticosteroid treatment. Total serum IgE levels sometimes return to within the normal range during the end-stage (67).

Approximately 40 epitopes able to bind the IgE molecule have been identified from *A. fumigatus*, alongside more than 20 recombinant allergens (named from Asp f 1 to Asp f 22) (63). Studies suggest that some of the recombinant allergens may be useful for discriminating between individuals with ABPA and those with AF-sensitized asthma (70). Kurup et al. have assessed the abilities of recombinant *Aspergillus* allergens (Asp f 1, f 2, f 3, f 4 and f 6) from the sera of ABPA patients and *A. fumigatus* sensitive asthmatics to bind to IgE. The number of recombinant allergens able to bind to the IgE antibody was higher in the sera from patients with ABPA than that from the asthmatics. Asp f 2, f 4 and f 6 interacted with IgE in all the ABPA patients tested. Such binding tests could therefore be used in ABPA diagnosis. In contrast, IgE antibody binding to Asp f 1 and f 3 was not specific. Hemmann et al. showed that skin prick tests with rAsp f 4 and rAsp f 6 provoked immediate skin reactions in patients with ABPA but not in controls and therefore allowed discrimination between ABPA and sensitization to *A. fumigatus* (71). Banerjee et al. showed that 70% of patients with ABPA had high levels of serum IgE antibodies to Asp f 16, a 43-kDa protein, whereas patients with positive AF skin test results did not (72). However at the time of the study, recombinant allergens were only available for research purposes and the data obtained needs to be confirmed.

Radiology and pulmonary function tests

Radiographic analyses have been carried out on chest X-rays and high resolution CT-scans. Certain abnormalities tend to be transient, such as pulmonary infiltrate, the presence of fluid in the bronchi and lobar or segmental collapse linked to mucous plugs (73). Permanent patterns included bronchiectasis, which was seen most frequently

in the upper lobes in the segmental and subsegmental bronchi, and cavities. Bronchiectasis occurs more centrally in ABPA patients than in those with other bronchial diseases. However, this central location is only suggestive of ABPA as bronchiectasis has been reported in the peripheral airways in some cases (74). Analysis using plain film revealed that most patients had upper lobe abnormalities (19/20; 95%), but 9/20 had both upper and lower lobe involvement (75). Descriptions of «glover-finger» opacities are common and correspond to bifurcating opacities caused by the bronchial distribution resulting from mucoid impaction. The collapse of a lobe segment, or entire lobes, has been described and was often associated with clinical exacerbation. Recurrence of mucoid impaction in these segments is not rare and may predispose the patient to bronchial damage.

Pleural effusion or calcification of mucoid impactions are rare but have been reported (76). Pulmonary fibrosis, pneumothorax and cavities occur during end-stage ABPA (74, 75, 77).

High resolution CT scan is more sensitive than chest X-ray for the detection of transient pulmonary infiltrate or bronchiectasis. Bronchiectasis patterns are described as cylindrical in most cases, but have also been referred to as cystic or varicous (77). The extent of the bronchiectasis is also usually defined (Fig. 2). Several studies have compared abnormalities in ABPA patients with those in *Aspergillus*-sensitive asthmatics (77–81). One of these studies showed that HRCT scan is more sensitive than radiography for diagnosing bronchiectasis (78). In this study, bronchiectasis was identified in 14/17 ABPA patients (82%), pleural thickening in 14 (82%) and atelectasis in 9 (64%) (78). However, patients with bronchiectasis and asthma do not necessarily have ABPA, although both conditions are present in about 80% of ABPA patients (77).

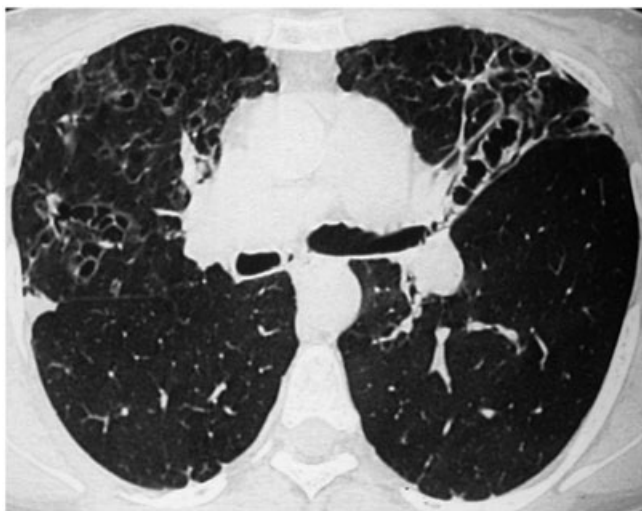


Figure 2. CT scan showing the diffuse cystic bronchiectasis responsible for lobar retraction of the left upper lobe.

Respiratory function tests (expiratory flow rates, lung volumes and diffusion capacities) are useful for diagnosis and during follow-up, but alone are not sufficient for monitoring treatment. Obstruction and restriction are both aggravated during acute exacerbations. Reductions in lung volume and diffusion capacity have been observed during exacerbations and in patients with end-stage ABPA (82). The severity of the obstruction in corticosteroid-dependent asthma (stage IV) varies depending on the patient (83–85). Deterioration of lung function also differs between ABPA patients; in some individuals lung function remains stable, whereas in others functional parameters progressively deteriorate in manner that is associated with the pattern of obstruction and restriction (86). Malo et al. compared the results of lung function tests on 20 asthmatic patients with ABPA with those of 20 asthmatics, paired in terms of sex, age and duration of asthma (87). All of the patients with ABPA and 75% of the patients with asthma alone showed significantly reduced FEV1. The FEV1 reversibility was more frequent in patients with asthma alone (50%) than in those with ABPA (31%), and the extent of this reversibility was also statistically greater in patients with asthma compared with those with ABPA (87).

Treatment

The long-term prognosis of ABPA is usually good, with most patients keeping a good respiratory status. Nevertheless, patients with 'refractory asthma' or bronchial destruction may have permanent airflow obstructions and/or severe restrictions. Detecting exacerbations is essential for limiting airway destruction, but the long-term use of systemic corticosteroids is not recommended, as there is no proof that this treatment prevents progressive bronchial destruction. In addition, exacerbations have been described in ABPA patients receiving high doses of oral corticosteroids (88), indicating that bronchial inflammation sensitive to corticosteroids is not the only factor involved in ABPA (89, 90). Bronchial colonization by fungal microorganisms represents an additional factor justifying the use of antifungal therapies. The goals of the treatment are:

- to limit exacerbations (requiring systematic testing for pulmonary infiltrates, which may or may not be associated with clinical symptoms);
- to eradicate colonization and/or proliferation of *A. fumigatus* in lumens with bronchiectasis and mucus plugs;
- to manage cortico-dependent asthma and fibrosis;
- thus, treatment appears to require two types of molecules: corticosteroids to treat the inflammatory response and antifungal agents to suppress or limit the proliferation of *A. fumigatus* and limit bronchial inflammation (91).

Oral corticosteroids

Systemic corticosteroids are currently the most effective treatment for the acute phase of ABPA. The recommended dose is 0.5 mg/kg/day for the first 2 weeks, followed by a progressive decrease in dose over the next 6–8 weeks. The treatment is monitored by assessing symptoms (fever, chest pain, hemoptysis, acute wheezing and sputum production), however, monitoring must also include a chest roentgenogram or HRCT scan, as infiltrates do not lead to clinical manifestations in a third of cases (92). Repeated dosages of total IgE serum levels are also recommended every 6–8 weeks during the first year after diagnosis, to determine a base-line value for each patient. Increases in total IgE serum levels of more than 100% above this base-line value indicate that the patient is at high risk of an exacerbation. The lung function tests recommended for asthma patients must also be performed as reductions in lung volume, diffusing capacity or exercise tolerance may be associated with an exacerbation.

Long-term systemic corticosteroid therapy is not recommended and thus assessment of these parameters is necessary for monitoring the treatment. If the patient has no new exacerbation within 6 months, he is judged to be in remission (stage II).

Stage IV patients have severe asthma, which is corticosteroid-dependent. In these cases, the minimal dose required to stabilize the patient must be identified. Treatment preventing corticosteroid-induced osteoporosis must also be proposed if necessary.

The extent of the bronchial destruction in stage V patients makes the prognosis poor. In addition, these patients suffer from recurrent infections (the majority of which involve *Pseudomonas*) and respiratory insufficiency with limited exercise tolerance. Treatment with corticosteroids is generally proposed, but is poorly efficient. Lee et al. (86) assessed 17 patients with stage V ABPA (fibrotic stage) for a mean observation period of 5 years. Roentgenographic infiltrates reoccurred in only one patient after the initial diagnosis. All patients required long-term prednisone therapy for controlling asthma. The prognosis was poor for patients with FEV1 of less than 0.8 l after the initial corticosteroid treatment.

Antifungal drugs

Several antifungal agents (e.g. amphotericin B, ketoconazole, clotrimazole, nystatin and natamycin) have been proposed as treatments for ABPA. However, no significant beneficial effects were observed when these drug treatments were tested and in several cases these agents were responsible for severe adverse effects (93).

In contrast, the new orally administered antifungal agent, *Itraconazole*, appears to be an effective adjunctive therapy for ABPA. We have conducted a preliminary retrospective clinical study comparing the outcome of a

1-year itraconazole treatment with that of 2-year therapy with the normal treatment of corticosteroids alone. Fourteen patients were included in this study and follow-up lasted for a period of 3 years. The following characteristics were compared: symptom scores, exacerbation frequencies, pulmonary function tests, total and AF-specific serum IgE levels, the amount of corticosteroid required during the first 2 years by the patients treated with these drugs alone and the amount required during the 1-year study period by patients being treated with the itraconazole-corticosteroid combination. The number of exacerbations was lower for the itraconazole-treated group than for the group treated with corticosteroids alone. Corticosteroid daily requirements decreased from 22 to 6.5 mg/day, although the dose required differed substantially between patients (88).

In addition, the results of a 16-week randomized double-blind trial of twice daily treatment with either 200 mg itraconazole or placebo, showed that itraconazole prevented disease progression in corticosteroid-dependent ABPA patients without any toxic effects (94). A positive response was defined as a reduction of at least 50% in corticosteroid dose, a decrease of at least 25% in serum IgE concentration, and one of the following: an improvement of at least 25% in exercise tolerance or pulmonary-function tests or the partial clearance or absence of pulmonary infiltrates. In a second phase of the same trial, consisting of an open-label study, all the patients received 200 mg of itraconazole per day for 16 additional weeks. In the double-blind phase of the trial 46% of the patients in the itraconazole group responded to the treatment, compared with 19% in the placebo group ($P = 0.04$). About one third (36%) of the patients who did not respond during the double-blind phase responded to treatment in the open-label phase of the trial, and none of the patients who responded in the double-blind phase of the trial had a relapse (94). The mechanisms underlying this treatment remain unclear. However, the results from a separate study suggest that itraconazole has an anti-inflammatory effect in ABPA patients tested (91).

The results from a randomized, double-blind, placebo-controlled trial performed using ABPA patients with stable symptoms ($n = 29$ and subjects received 400 mg of itraconazole ($n = 15$) or placebo ($n = 14$) per day for 16 weeks) demonstrated that itraconazole treatment reduced eosinophilic airway inflammation, systemic immune activation and the number of exacerbations (91). These results indicate that itraconazole could be used as an adjunctive treatment for ABPA.

Meta-analysis of the data available (mainly three prospective, randomized and controlled studies) led to the conclusion that itraconazole modifies the immunologic activation associated with ABPA and improves clinical outcome, at least over a period of 16 weeks (Cochrane Airways Group Asthma Trials Register) (95). Adrenal suppression caused by the inhalation of

corticosteroids and itraconazole treatment is a potential concern. On the one hand, treatment with this antifungal agent reduces bronchial inflammation and may prevent bronchial destruction and exacerbation in stable ABPA patients. It also improves the clinical status of corticosteroid-dependent-ABPA patients. On the other hand, long-term prescription of an antifungal therapy may lead to resistance. The trials validating the use of itraconazole in ABPA patients used a dose of 200 mg/day, administered for a duration of 16 weeks (95).

The impact of long-term exposure to *Aspergillus* present in the environment is uncertain (47), but direct exposure to high concentrations of this fungus should be avoided. Fiberoptic bronchoscopy may be necessary to

remove the mucoid impaction responsible for atelectasis in rare cases where it is refractory to corticosteroid treatment.

In conclusion, ABPA is a common manifestation in chronic allergic asthma and cystic fibrosis patients. Despite the high frequency of the disease among these patients, diagnoses are not generally made until a long time after the initiation of the asthmatic disease. When the clinical, radiological and biological criteria for ABPA appear in combination and the diagnosis is made, a treatment that includes both corticosteroids and the antifungal agent, itraconazole, needs to be administered. However, the treatment regimes for this antifungal therapy have yet to be definitely established.

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