

Pathophysiology and immunology of allergic bronchopulmonary aspergillosis

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Allergic bronchopulmonary aspergillosis (ABPA) is a complication of persistent asthma and cystic fibrosis (CF), diseases in part characterized by excessive viscous mucus and compromised mucociliary clearance. Inhaled conidia of *Aspergillus fumigatus* are able to persist and germinate, releasing exoproteases and other fungal products that further compromise clearance, breach the epithelium, and activate immune responses. Chemotactic cytokines (e.g. IL-8, RANTES, eotaxin) in particular have been implicated in murine models. Chemokine-mediated recruitment of CD4+T_H2 lymphocytes specific for *A. fumigatus* is a crucial feature of ABPA. Susceptibility also appears to involve immunogenetic factors including atopy and defined major histocompatibility complex-restricted allelic expression on antigen-presenting cells that are permissive for a T_H2-predominant immune response. Certain *A. fumigatus* allergens appear more associated with ABPA rather than simple *A. fumigatus* allergy. ABPA is characterized by marked local and systemic eosinophilia, an adaptive immune response with elevated levels of *A. fumigatus*-specific IgG, IgA and IgE antibodies, and a profound nonspecific IL-4-dependent elevation in total IgE. Clinically, ABPA manifests with recurring episodes of asthma, pulmonary infiltrates, and central bronchiectasis that may progress to fibrosis. It is treated with systemic glucocorticoids and azoles. Monitoring clinical, radiographic and serologic responses (especially total IgE) is essential for successful management.

Keywords *Aspergillus fumigatus*, aspergillosis, bronchiectasis, cystic fibrosis, chemokines

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an important complication of persistent asthma (1–2% prevalence) and cystic fibrosis (CF) (prevalence 5%–15%) [1]. It does not occur in healthy individuals and only very rarely in other diseases that are themselves rare (such as chronic granulomatous disease or hyper-IgE syndrome). Asthma and CF are chronic inflammatory airway diseases characterized in part by excessive and pathologically viscous mucus secretion and

compromised mucociliary clearance, but the susceptibility of a minority of these patients to develop ABPA is only partly understood.

Risk factors

Predisposing factors are thought to include atopy, immunogenetic HLA-restricted phenotypes, mutations in the cystic fibrosis transmembrane conductance regulator [CFTR] gene, polymorphisms of the collagen region of the surfactant protein A2 and probably other collectins such as mannose-binding lectin, perhaps physicochemical characteristics of respiratory secretions and environmental exposure history [1–3].

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Pathogenesis

Whatever the constellation of predisposing factors, in some patients with persistent asthma or CF, inhaled conidia of *Aspergillus fumigatus* and occasionally other *Aspergillus* species are able to persist and germinate, leading to growth of hyphae in mucus plugs which may be seen in expectorated sputum. This process releases *A. fumigatus* exoproteases and other secreted and cytoplasmic fungal products that are capable of further compromising mucociliary clearance, breaching the airway epithelial barrier, and activating the innate immune system of the lung, including epithelial production of several cytokines [4].

The role of chemotactic cytokines (chemokines) in particular has been pathogenetically implicated in murine models of chronic allergic airway inflammation that in many ways are similar to human ABPA [5,6]. Chemokines implicated in up- or down-regulating the chronic allergic response to *A. fumigatus* in murine knockout models include monocyte chemoattractant protein-1 (MCP-1/CCL2), eotaxin (CCL11), regulated on activation, normal T cell expressed and secreted (RANTES/CC15), interleukin-8 (IL-8/CXCL8), and macrophage inflammatory protein-1 α (MIP-1 α /CCL3) [7].

It is thought that chemokine-mediated recruitment of CD4⁺ T_H2 lymphocytes specific for *A. fumigatus* epitopes to the regional airways adjacent to impacted *A. fumigatus* hyphae-containing mucus plugs is a crucial feature of ABPA. *A. fumigatus*-reactive CD4⁺ T_H2 cell lines and clones can be easily isolated from peripheral circulation of ABPA patients but not controls [2,8].

Immunogenetic factors skewing the immune response to T_H2 polarization include the pattern of chemokine secretion and responsiveness, atopy, and major histocompatibility complex-restricted phenotype expression on antigen-presenting cells (e.g. specific HLA DR 2/5 alleles) [9]. Several cytoplasmic *A. fumigatus* allergens, especially *Asp f3* and *Asp f4*, appear more closely associated with ABPA rather than simple IgE-mediated *A. fumigatus* allergy [10].

Immunopathologically ABPA is characterized by a marked local and systemic eosinophilia, and probable local neutrophilia, with release of granular exoproducts such as eosinophil major basic protein, eosinophil cationic protein and neutrophil gelatinase B (matrix metalloproteinase-9) [11,12]; a specific humoral adaptive immune response with elevated local levels of *A. fumigatus*-specific IgG, IgA and IgE antibodies; and a profound systemic polyclonal (nonspecific) IL-4-dependent elevation in total IgE levels. Circulating B

cells of ABPA patients show enhanced activation markers such as the co-stimulatory ligand CD86 and interleukin-2 receptor expression, increased expression and shedding of CD23 (Fc ϵ RII), and increased sensitivity to IL-4 [13]. The immune response is utilized diagnostically with serologic assessment of circulating total IgE, *A. fumigatus*-specific IgE antibodies, *A. fumigatus*-specific IgG or precipitating antibodies, and peripheral eosinophilia.

Questions of allergen and assay standardization, and defining optimal disease-specific cutoff values, still bedevil the use of serology to independently make a diagnosis of ABPA. There is thus great interest in applying recombinant *A. fumigatus* allergens to serodiagnosis. ABPA patients show increased IgE reactivity to *Asp f2*, *Asp f3*, *Asp f4*, *Asp f6* and *Asp f16* compared with *A. fumigatus*-allergic non-ABPA patients [10].

Pathology

The pulmonary pathology of ABPA, particularly the development of bronchiectasis, is most likely due to effects of local granulocyte accumulation, activation and ongoing release of toxic exoproducts. Histopathologically, central bronchiectasis is the most common finding, but other histopathologic abnormalities may include eosinophilic pneumonitis, bronchocentric granulomatosis, exudative or obliterative bronchiolitis, interstitial pneumonitis, vasculitis, and hyphae-laden microabscesses [11].

Diagnosis

Diagnosis of ABPA in asthmatics requires a minimum of five of the following criteria: underlying asthma; proximal bronchiectasis; positive immediate *A. fumigatus* skin test; elevated serum IgE *A. fumigatus* antibody; elevated serum total IgE (>417 U/mL or 1000 ng/mL); elevated serum IgG *A. fumigatus* antibody; positive *A. fumigatus* precipitins; and pulmonary infiltrates on chest imaging [14]. In CF, these criteria have been modified as there are aspects of underlying CF that overlap with ABPA, and include the following: clinical and/or pulmonary function deterioration from baseline status; positive immediate *A. fumigatus* skin test or elevated serum IgE *A. fumigatus* antibody; elevated serum total IgE >1000 U/mL; elevated serum IgG *A. fumigatus* antibody or positive *A. fumigatus* precipitins; and abnormal chest imaging findings or change in baseline abnormalities [2]. Chest CT imaging has been a valuable advance in imaging for diagnosing ABPA, but no finding is pathognomonic. Besides

central bronchiectasis, one may commonly see bronchial wall thickening, focal air trapping, mucus plugging, atelectasis, fibrosis, or cavitation [2,14].

Clinical features and screening

Clinically ABPA manifests with wheezing, bronchial hyperreactivity, pulmonary infiltrates, and bronchiectasis that may progress to fibrosis. Bronchiectasis results in chronic bronchorrhea, productive cough which may include brown plugs containing hyphae, episodes of systemic illness with fever and malaise, and sometimes hemoptysis. Concomitant wheezing and dyspnea also occur in patients with either underlying asthma or CF. Monitoring of clinical, radiographic and serologic responses, especially total serum IgE (which is rapidly responsive to effective pharmacotherapy) is essential for successful management.

In patients with CF, where the risk of ABPA is highest, screening for ABPA by annual monitoring of serum total IgE levels should begin at school age [2]. If total IgE is >500 U/mL, testing for *A. fumigatus* allergy by skin test or *A. fumigatus*-specific IgE should be performed. If IgE is elevated but <500 U/mL, patients should be followed closely and IgE level repeated if clinical suspicion is high.

Staging

Five stages of ABPA have been identified: acute (I); remission (II); exacerbation (III); corticosteroid-dependent (IV); and fibrotic or end stage (V). Total IgE levels and imaging results vary in the different stages. IgE levels may be normal or at pre-ABPA baseline levels in stages II, IV or V. Pulmonary infiltrates may be absent in stages II or IV [14].

Treatment

Treatment of ABPA relies primarily on use of 1–2 week burst (≥ 0.5 mg/kg daily) followed by slow taper (several months of alternate day dosing) regimens of systemic glucocorticosteroids, usually prednisone [2,14]. Increasingly itraconazole, an azole antifungal active against *A. fumigatus*, has been employed as adjunctive antigen burden-reduction therapy in ABPA patients with relapse, corticosteroid-dependence, or steroid toxicity. Double-blind placebo-controlled randomized trials of itraconazole have shown benefit in asthmatic ABPA, while uncontrolled trials have suggested similar benefit in CF ABPA [2,15]. There are no data as yet regarding the newer azole agent voriconazole. While voriconazole is active against *A. fumigatus*

and offers better bioavailability than itraconazole, it is much more expensive, has a higher adverse event profile, and has not been studied in clinical trials for ABPA. Other approaches including use of inhaled steroids or amphotericin B have been used in certain instances but not sufficiently studied in clinical trials.

Monitoring of treatment efficacy and toxicity is imperative. Total serum IgE levels usually decrease by at least one-third over six weeks from the initiation of treatment, infiltrates resolve after 1–2 months, and pulmonary function tests show improvement [2,14].

It is also important to identify and remediate environmental *A. fumigatus* exposure hazards. Patients can be counseled about outdoor *A. fumigatus* exposure hazards such as working with decomposing organic materials, and indoor spore levels lowered with proper decontamination and use of HEPA filters.

Traditional allergen injection immunotherapy has not been shown to be of value in treating ABPA, but newer approaches to encourage immune deviation toward T_H1 responses using synthetic *A. fumigatus* peptides, DNA-based vaccines, and immunostimulatory sequences such as cytosine polyguanine oligonucleotides are being explored in animal models [6].

When itraconazole is employed and clinical response is suboptimal it may be helpful to determine steady-state itraconazole levels (i.e. drawn 4 hours after a dose after 1–2 weeks of treatment) to document adequate absorption, which may be a particular problem in CF patients. Itraconazole bioavailability can be improved with use of gastric pH-lowering strategies such as concomitant meal or cola, pre-dosing itraconazole before acid-suppressing agents, or switching to the more bioavailable liquid formulation [2]. Voriconazole may have an advantage in this situation. Drug-drug interactions must be considered. For example, enhanced cyclosporine levels due to inhibition of hepatic CYP3A4 by itraconazole, and adrenal suppression in patients on itraconazole treated with concomitant inhaled budesonide, been well documented [16].

With timely diagnosis and appropriate therapy ABPA is a treatable, non-progressive illness, but it is also difficult to recognize and is a troublesome disease that usually recurs, causing acute or subacute exacerbations, and therefore needs long-term vigilance.

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