Allergic and Noninvasive Infectious Pulmonary Aspergillosis Syndromes

Eavan G. Muldoon, MD, MPH[a,b,*], Mary E. Strek, MD[c], Karen C. Patterson, MD[d]

KEYWORDS

• Aspergillus • ABPA • Aspergillus bronchitis • Chronic fungal infection of lung

KEY POINTS

- Allergic bronchopulmonary aspergillosis (ABPA) is a hyperimmune response to the presence of fungi in the airway in patients with asthma, which leads to permanent airway damage and often requires immunosuppression for adequate treatment.
- As a result of defects in immune clearance and mechanical clearance, patients with cystic fibrosis (CF) are particularly vulnerable to developing ABPA, which may hasten their clinical decline.
- In severe asthma with fungal sensitization (SAFS), exposures to fungi can account for asthma exacerbations; the diagnosis often requires escalation to maximal asthma therapy.
- Chronic pulmonary aspergillosis (CPA) is a spectrum of noninvasive infectious aspergillus diseases, which range from simple nodules to indolent aspergillomas to progressive cavitating and fibrotic lung disease.
- A diagnosis of aspergillus bronchitis should be considered in patients with lingering bronchitis symptoms and repeatedly positive fungal cultures.

INTRODUCTION

Despite the ubiquity of *Aspergillus* spp and that the spores are inhaled daily, only a small proportion of the population develops clinical disease. *Aspergillus* spp can cause a spectrum of disease from allergy, which does not represent true infection, to colonization, chronic infection, and finally invasive disease.[1] This article reviews the noninvasive *Aspergillus* syndromes, focusing on clinical presentation, diagnosis, management, and potential complications.

ALLERGIC ASPERGILLOSIS

Allergic Bronchopulmonary Aspergillosis

ABPA occurs almost exclusively in patients with asthma or CF, where fungal sensitization elicits a robust hypersensitivity response characterized by elevated total serum immunoglobulin (Ig) E and *Aspergillus*-specific IgE and IgG antibodies (**Table 1**). ABPA is estimated to occur in 2.5% of patients with asthma and should be suspected in patients with difficult to control or corticosteroid dependent disease or in those who expectorate

Disclosure Statement: The authors have nothing to disclose.

[a] National Aspergillosis Centre, University Hospital of South Manchester, Southmoor Road, Wythenshawe, Manchester M23 9LT, UK; [b] Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK; [c] Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, 5481 S. Maryland Avenue, Chicago, IL 60637, USA; [d] Division of Pulmonary, Allergy and Critical Care, University of Pennsylvania, 3400 Spruce Street, 828 West Gates Building, Philadelphia, PA 19104, USA

* Corresponding author. National Aspergillosis Centre, University Hospital of South Manchester, Southmoor Road, Wythenshawe, Manchester M23 9LT, United Kingdom.

E-mail address: eavan.muldoon@manchester.ac.uk

Clin Chest Med ■ (2017) ■–■

http://dx.doi.org/10.1016/j.ccm.2017.04.012

Table 1
Features of allergic aspergillus pulmonary diseases

Subtype	Defining Clinical Features	Diagnostic Immunologic Features	Treatment
ABPA in asthma	Persistent or escalating asthma symptoms and bronchiectasis (+/− mucus plugging and tree in bud changes) noted on chest imaging; fungal cultures may be positive for *Aspergillus spp*.	• Markedly elevated total IgE • Positive skin prick testing and/or elevated serum aspergillus-specific IgE levels • +/− Elevated aspergillus-specific IgG levels • Eosinophilia is common but not required	• Systemic corticosteroids • ICS, Bronchodilators • Trial of antifungal agents in some cases • +/− Omalizumab • Fungal avoidance if high antigen exposure
ABPA in CF	Similar to non-CF ABPA + progressive pulmonary decline, which can be permanent.	Similar to non-CF ABPA.	Similar to non-CF ABPA
SAFS	Asthma requiring high-dose ICS and often an additional controller medication + fungal sensitization; does not meet criteria for ABPA.	Positive skin prick and/or elevated serum antifungal IgE levels.	• Maximum inhaler therapy • +/− Omalizumab • Antifungal agents remain investigational

Abbreviation: ICS, inhaled corticosteroids.

mucus plugs or demonstrate bronchiectasis and/or mucus plugging on chest imaging.[2–4] It is important to establish the diagnosis of ABPA because this has an impact on therapy and potentially reduces morbidity and complications that might otherwise ensue.

Diagnosis of allergic bronchopulmonary aspergillosis

Diagnostic criteria for ABPA have been updated recently after a conference of the International Society for Human and Animal Mycology.[5] Although they have yet to be formally validated, neither were the previous proposed criteria they replaced. The updated criteria include (1) a predisposing underlying condition of either asthma or CF, (2) an elevated total IgE level greater than 1000 IU/mL AND either a positive *Aspergillus* skin test or detectable *Aspergillus fumigatus*–specific IgE, and (3) at least 2 of the following 3 criteria of serum precipitating or *Aspergillus*–specific IgG antibodies, characteristic radiographic findings, and elevated total eosinophil count (see **Table 1**). These criteria allow patients to be diagnosed with ABPA in the absence of radiographic changes. Recent administration of systemic corticosteroids may decrease total IgE levels and/or eosinophil counts, thus obscuring the diagnosis. A recent prospective study of *Aspergillus*-specific IgG levels in 102 treatment-naive patients with ABPA compared with 48 controls found these IgG antibodies to be useful in the diagnosis of ABPA, with a sensitivity and specificity of 89% and 100%, respectively.[6] IgG levels were unreliable, however, for monitoring treatment response.

ABPA should be suspected in patients who have worsening asthma despite conventional therapy or require systemic corticosteroids. Although ABPA may be suggested by chest x-ray findings, a high-resolution CT (HRCT) may better detect the radiographic features of ABPA.[5] Transient radiographic findings include consolidation, nodules, tram-track opacities, and finger-in-glove and other fleeting opacities. Permanent changes include bronchiectasis that is often central, pleuropulmonary fibrosis, and parallel lines and ring shadows.

The Infectious Diseases Society of America practice guidelines on aspergillosis recommend screening for APBA in asthma patients on an annual basis, especially in those with frequent exacerbations.[4] Recommended screening is with *A fumigatus*–specific IgE levels.[5] If positive, a total serum IgE level should be sent. If the level is greater than 1000 IU/mL, an *Aspergillus* skin test, peripheral eosinophil count, *A fumigatus* precipitins, and/or specific IgG level should be obtained. If 2 of 4 of these tests are positive, an HRCT is performed. If the HRCT is normal, a diagnosis of seropositive ABPA is made.