Allergic Bronchopulmonary Aspergillosis

An Overview

Dani S. Zander, MD

• This article provides an overview of the major pathologic manifestations of allergic bronchopulmonary aspergillosis; patient characteristics; clinical, radiographic, and laboratory features of the disease; and current knowledge about its pathogenesis. Although allergic bronchopulmonary aspergillosis is an infrequent complication of asthma or cystic fibrosis, recognition of this disorder is important to avoid progression of bronchiectasis and lung parenchymal damage. Clinical, laboratory, and radiographic criteria allow for diagnosis of most cases, but the pathologist may encounter clinically unsuspected or atypical cases that require morphologic confirmation.

(*Arch Pathol Lab Med.* 2005;129:924–928)

Aspergillus is a genus of fungi with a worldwide distribution. This fungus is found in decomposing organic matter and can colonize walls and ceilings where water damage has occurred.[1] Of the approximately 180 officially recognized species of *Aspergillus*, a relatively small number serve as causes of human disease.[2] *Aspergillus fumigatus*, *A flavus*, and *A niger* are the most common human pathogens. Pulmonary *Aspergillus* infection is initiated by inhalation of airborne spores that are small enough (2–3 μm) to reach the alveoli. Inhalation of spores is not by itself sufficient to cause disease, however. Host characteristics or predisposing factors are usually present to account for a heightened susceptibility to disease.

Aspergillus infection can lead to multiple clinicopathologic syndromes (Table), and progression from a less aggressive to a more aggressive form rarely occurs.[3] In this spectrum of syndromes, disease manifestations arise from varying combinations of direct tissue injury by the fungi and endogenous immunologic responses. Host immunologic responses are central to the pathogenesis of allergic bronchopulmonary aspergillosis (ABPA) and hypersensitivity pneumonia, whereas direct tissue injury by the fungi plays a more important role in invasive pneumonia. Although *A fumigatus* is the most common *Aspergillus* species to trigger ABPA, *A niger*, *A flavus*, *A nidulans*, *A oryzae*, and *A terreus* have occasionally been responsible for this condition, and more than 1 species can be isolated in rare cases.[4–6]

PATHOLOGIC FEATURES

In ABPA, airway colonization by *Aspergillus* exacerbates underlying asthmatic airway injury. Persistent airway inflammation and fibrosis with destruction of bronchial structural elements leads to bronchiectasis and parenchymal scarring. Pathologic manifestations of ABPA include mucoid impaction of bronchi, bronchocentric granulomatosis, eosinophilic pneumonia, and chronic or exudative bronchiolitis.[7–9] In mucoid impaction of bronchi, bronchial lumens are filled and distended by mucus and inflammatory cells, which may be organized as allergic mucin (Figures 1 through 3). Allergic mucin is recognized by its layered pattern of cells, cellular debris, and mucus. Cells include histologically viable and necrotic eosinophils and other inflammatory cells, and cellular debris is often abundant. Charcot-Leyden crystals can be prominent, but fungal hyphae are often difficult to find, even with histochemical stains, and they are often fragmented (Figures 3 and 4). Bronchial wall invasion by fungi is usually absent, but the bronchial wall is inflamed. Asthmatic changes are often present, including a polymorphous inflammatory infiltrate of eosinophils, lymphocytes, and plasma cells; airway epithelial injury or goblet cell hyperplasia, squamous metaplasia, and ulceration; and thickening of the basement membrane (Figure 5). Muscular and cartilaginous loss and fibrosis often accompany these inflammatory changes.

It should also be noted that ABPA is not the sole cause of mucoid impaction. Mucoid impaction can also develop in association with obstructing bronchial lesions, including neoplasms and tuberculosis, but ideally, histologic features of these other processes will indicate their existence to the surgical pathologist.

The pattern of distal airway replacement by necrotizing granulomas centered upon the airway lumens is referred to as bronchocentric granulomatosis (Figure 6). An elastic stain can be helpful for showing the airway-centered location of the granulomas (Figure 7). Although *Aspergillus* hyphae can be found in the necrotizing granulomas, they are usually sparse and fragmented. Bronchioles may also demonstrate mixed inflammatory infiltrates including eo-

Accepted for publication March 15, 2005.

From the Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at Houston Medical School.

Presented in part at the Pulmonary Specialty Conference at the 94th Annual Meeting of the United States and Canadian Academy of Pathology, San Antonio, Tex, March 2005.

The author has no relevant financial interest in the products or companies described in this article.

Reprints: Dani S. Zander, MD, Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at Houston Medical School, 6431 Fannin, Room MSB 2.258, Houston, TX 77030 (e-mail: Dani.S.Zander@uth.tmc.edu).

Forms of *Aspergillus*-Related Lung Disease	
Clinicopathologic Syndrome	**Patient Characteristics**
Allergic bronchopulmonary aspergillosis	Asthma, cystic fibrosis, rarely hyper–immunoglobulin E syndrome or chronic granulomatous disease
Aspergilloma	Preexisting cavity or bronchiectasis
Hypersensitivity pneumonia	Sensitivity to *Aspergillus* antigens
Chronic necrotizing (semi-invasive) aspergillosis	Chronic lung disease or mild immunocompromise
Invasive tracheobronchial aspergillosis	Usually significant immunocompromise; rarely, a localized form can occur in patients with lesser degrees of immunocompromise
Invasive *Aspergillus* pneumonia	Significant immunocompromise

sinophils, allergic mucin, or obliterative bronchiolitis. Bronchocentric granulomatosis is also not restricted to ABPA; it can be a response to pulmonary infection with mycobacteria, other types of fungi, or *Echinococcus*.

Other potential manifestations of ABPA include eosinophilic pneumonia, characterized by alveolar infiltrates of eosinophils and macrophages (Figure 8); rarely aspergilloma[10]; and secondary postobstructive changes including acute or organizing bacterial pneumonia, abscess formation, lipoid pneumonia, and chronic interstitial pneumonia.

PATIENT CHARACTERISTICS

Asthma, cystic fibrosis, or both are present in most patients with ABPA, although findings of ABPA occasionally occur in individuals without clinical symptoms of these disorders.[11] In patients with persistent asthma, the incidence of ABPA is approximately 1% to 2%, and approximately 7% (range, 1%–15%) of patients with cystic fibrosis meet criteria for ABPA.[12–15] Patients with the congenital immunodeficiency syndromes of hyper–immunoglobulin (Ig) E syndrome and chronic granulomatous disease may be at increased risk for ABPA.[16] In addition, higher frequencies of specific *HLA-DR2* and *HLA-DR5* genotypes are found in association with ABPA.[17]

CLINICAL, RADIOGRAPHIC, AND LABORATORY FEATURES

Patients with ABPA often experience a worsening of asthmatic symptoms.[18] Expectoration of brown mucus plugs can occur with mucoid impaction, assisting in diagnosis by providing a sample that can be stained and cultured.[3] Allergic bronchopulmonary aspergillosis often has its onset in childhood and can remain occult for long periods before the diagnosis is made.[19] Therapy is geared to reducing inflammation and immunologic activity. Corticosteroids and antifungal agents are used to reduce airway inflammation and decrease fungal colonization of airways.

Clinical, radiographic, and laboratory features of ABPA include the following: presence of asthma; current or previous pulmonary infiltrates; central bronchiectasis; peripheral blood eosinophilia; immediate cutaneous reactivity to *Aspergillus*; elevated total serum IgE concentration; serum precipitating antibodies to *A fumigatus*; and elevated serum antibodies of IgE, IgG, or both to *A fumigatus*.[15,19–22] All of these criteria do not need to be present to diagnose ABPA. In an individual with central bronchiectasis, the essential criteria include asthma, immediate cutaneous reactivity to *Aspergillus* antigens, and serum IgE level greater than 417 IU/mL. Without central bronchiectasis, individuals are labeled as ABPA-seropositive if they have asthma, immediate cutaneous reactivity to *Aspergillus*, serum IgE level greater than 417 IU/mL, history of radiographically compatible pulmonary infiltrates, and elevated levels of serum IgE and IgG antibodies to *A fumigatus*.[20]

Most patients with ABPA will be diagnosed based on clinical, radiographic, and laboratory criteria. Lung biopsy is usually not required for diagnosis, but it can be important for patients with atypical presentations. In these patients, recognition of allergic mucin and fungal hyphae can offer support for a diagnosis of ABPA.[23] Also, ABPA may represent an unsuspected diagnosis in the occasional patient who undergoes bronchoscopy for a lung mass that is discovered to be mucoid impaction.

In a setting of cystic fibrosis, diagnosis of ABPA can be difficult because of the overlap of many of the diagnostic criteria with common manifestations of cystic fibrosis.[15] Proposed minimal criteria for diagnosis of ABPA in cystic fibrosis include acute or subacute clinical deterioration not attributable to another etiology; total serum IgE concentration of greater than 500 IU/mL; immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE antibodies to *A fumigatus*; and either precipitins or IgG antibodies to *A fumigatus* or new or recent pulmonary infiltrates, mucus plugging, or bronchiectasis that have not cleared with antibiotics and physiotherapy.[15]

PATHOGENESIS OF ABPA

In ABPA, host immune responses and direct fungal injury lead to airway injury and fibrosis. Fungal proteases damage airway epithelial cells, which facilitates antigen transport across the epithelial cell layer, and interactions of *Aspergillus* antigens with airway epithelial cells prompt release of proinflammatory cytokines and chemokines that initiate an immunologic/allergic inflammatory response.[24,25] The fungus induces a Th2-type response with elevated *Aspergillus*-specific and total serum IgE levels and prominent eosinophilic infiltration.[26] Epithelial cell release of growth factors is promoted by the Th2-type cytokines interleukin 4 and interleukin 13, and repair and remodeling proceeds to create the bronchiectatic lesions characteristic of ABPA.[24]

OTHER FUNGI CAUSING ALLERGIC BRONCHOPULMONARY FUNGAL DISEASES

Clinicopathologic syndromes resembling ABPA can be caused by other fungi (allergic bronchopulmonary fungal disease or allergic bronchopulmonary mycosis), including *Candida albicans*, *Curvularia* species, *Helminthosporium* spe-

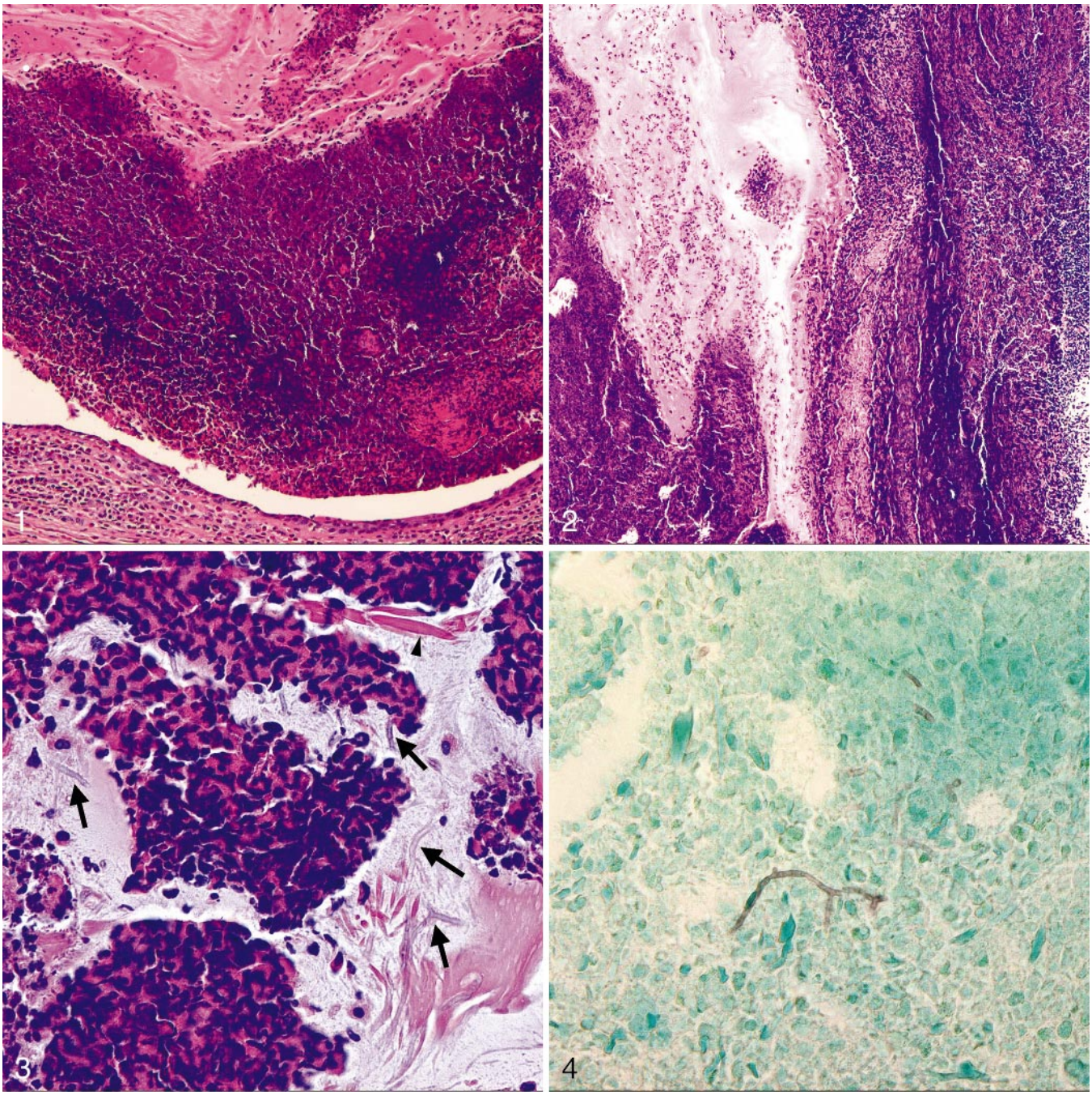

Figure 1. *The bronchial lumen is filled with numerous inflammatory cells, cellular debris, mucus, and fibrinous material (hematoxylin-eosin, original magnification ×100).*

Figure 2. *Layered mucus and inflammatory cells and debris occupy the lumen of a bronchus (hematoxylin-eosin, original magnification ×100).*

Figure 3. *Multiple aggregates of eosinophils and Charcot-Leyden crystals (arrowhead) are present in a background of mucus. Several fungal hyphae (arrows) with features of* Aspergillus *are also seen (hematoxylin-eosin, original magnification ×200).*

Figure 4. *Small numbers of fragmented hyphae lie in the inflammatory exudate. Cultures yielded* Aspergillus flavus *(methenamine silver stain, original magnification ×400).*

cies, *Torulopsis glabrata*, *Bipolaris* species, *Cladosporiosis* species, *Saccharomyces cerevisiae*, *Schizophyllum commune*, and *Tricosporon beigelii*.[5,11,27–41] If cultures, skin tests, and antibody assays for *Aspergillus* are negative despite clinical and radiographic features suggestive of ABPA, a fungal cause other than *Aspergillus* should be considered in the differential diagnosis.

SUMMARY

Allergic bronchopulmonary aspergillosis is most often a complication of asthma or cystic fibrosis. Although the diagnosis will usually be determined based upon a combination of clinical, laboratory, and radiographic criteria, occasional examples will require pathologic diagnosis. Rec-

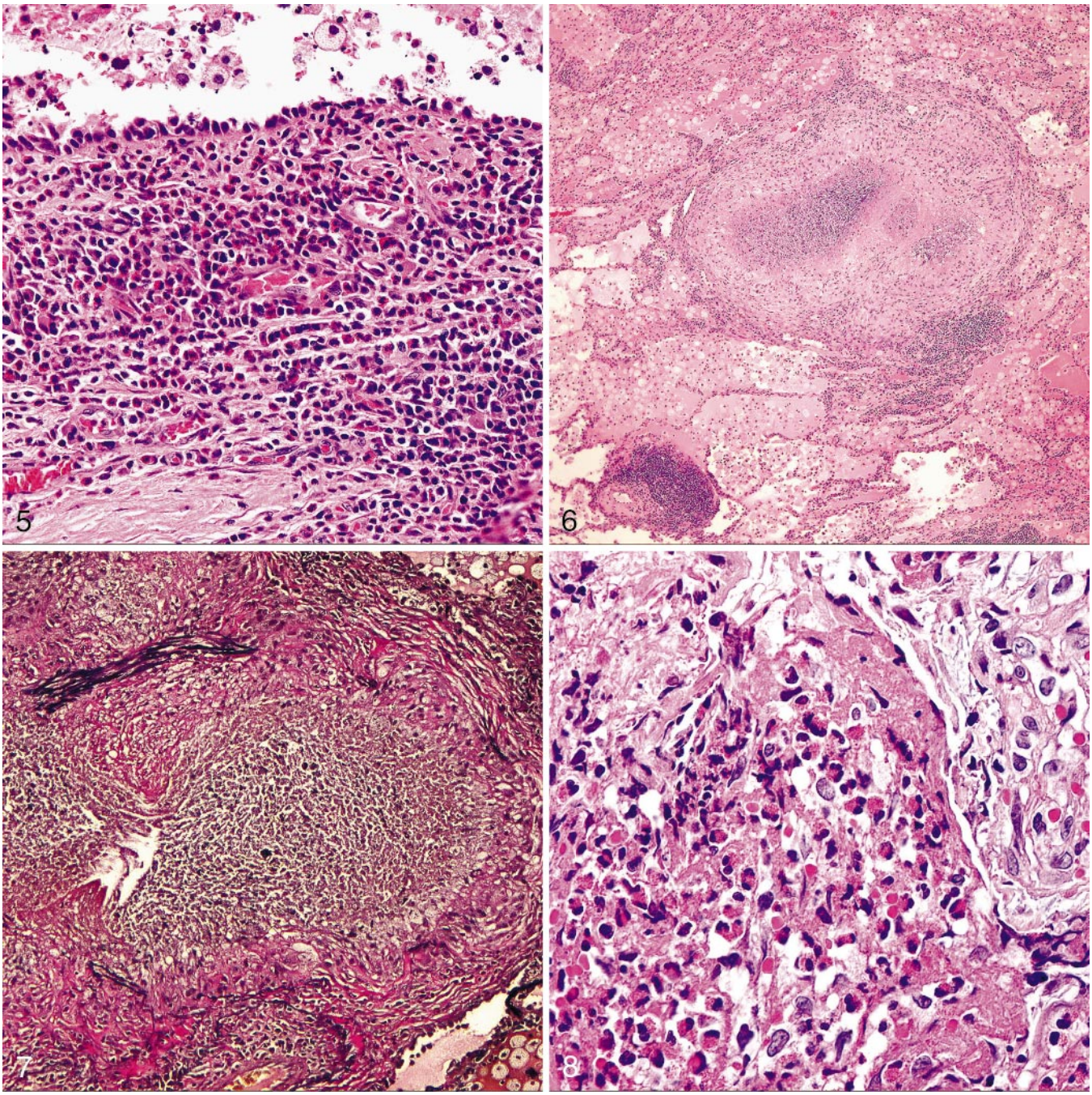

Figure 5. *The bronchial mucosa contains dense infiltrates of mixed inflammatory cells, including numerous eosinophils. There is partial loss of epithelial cells (hematoxylin-eosin, original magnification ×200).*

Figure 6. *Airways are replaced by necrotizing granulomatous inflammation (hematoxylin-eosin, original magnification ×100).*

Figure 7. *This elastic stain highlights some residual elastic fibers from the original airway, which has been largely destroyed by a granuloma (elastic van Gieson, original magnification ×200).*

Figure 8. *The alveolar space contains numerous eosinophils and fewer macrophages in a background of fibrinous material (hematoxylin-eosin, original magnification ×400).*

ognition of the major manifestations (mucoid impaction, bronchocentric granulomatosis, eosinophilic pneumonia) of this disorder will assist in the detection and pathologic diagnosis of this condition. Diagnosis of the process is important so that therapy can be instituted to prevent or ameliorate the advancement of the lung disease.

References

1. Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol.* 2002;110:685–692.
2. Marr KA, Patterson T, Denning D. Aspergillosis: pathogenesis, clinical manifestations, and therapy. *Infect Dis Clin North Am.* 2002;16:875–894.
3. Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. *Chest.* 2002;121:1988–1999.
4. Chakrabarti A, Sethi S, Raman DS, Behera D. Eight-year study of allergic

bronchopulmonary aspergillosis in an Indian teaching hospital. *Mycoses.* 2002; 45:295–299.

5. Sandhu RS, Mehta SK, Khan ZU, Singh MM. Role of *Aspergillus* and *Candida* species in allergic bronchopulmonary mycoses: a comparative study. *Scand J Respir Dis.* 1979;60:235–242.

6. Akiyama K, Takizawa H, Suzuki M, Miyachi S, Ichinohe M, Yanagihara Y. Allergic bronchopulmonary aspergillosis due to *Aspergillus oryzae*. *Chest.* 1987; 91:285–286.

7. Sulavik SB. Bronchocentric granulomatosis and allergic bronchopulmonary aspergillosis. *Clin Chest Med.* 1988;9:609–621.

8. Bosken CH, Myers JL, Greenberger PA, Katzenstein AL. Pathologic features of allergic bronchopulmonary aspergillosis. *Am J Surg Pathol.* 1988;12:216–222.

9. Katzenstein AL, Liebow AA, Friedman PJ. Bronchocentric granulomatosis, mucoid impaction, and hypersensitivity reactions to fungi. *Am Rev Respir Dis.* 1975;111:497–537.

10. Rosenberg IL, Greenberger PA. Allergic bronchopulmonary aspergillosis and aspergilloma: long-term follow-up without enlargement of a large multiloculated cavity. *Chest.* 1984;85:123–125.

11. Glancy JJ, Elder JL, McAleer R. Allergic bronchopulmonary fungal disease without clinical asthma. *Thorax.* 1981;36:345–349.

12. Greenberger PA. Clinical aspects of allergic bronchopulmonary aspergillosis. *Front Biosci.* 2003;8:s119–s127.

13. Geller DE, Kaplowitz H, Light MJ, Colin AA, for the Scientific Advisory Group, Investigators, and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Allergic bronchopulmonary aspergillosis in cystic fibrosis: reported prevalence, regional distribution, and patient characteristics. *Chest.* 1999;116:639–646.

14. Moss RB. Allergic bronchopulmonary aspergillosis. *Clin Rev Allergy Immunol.* 2002;23:87–104.

15. Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis: state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis.* 2003;37(suppl 3):S225–S264.

16. Eppinger TM, Greenberger PA, White DA, Brown AE, Cunningham-Rundles C. Sensitization to *Aspergillus* species in the congenital neutrophil disorders chronic granulomatous disease and hyper-IgE syndrome. *J Allergy Clin Immunol.* 1999;104:1265–1272.

17. Chauhan B, Santiago L, Kirschmann DA, et al. The association of HLA-DR alleles and T cell activation with allergic bronchopulmonary aspergillosis. *J Immunol.* 1997;159:4072–4076.

18. Fink JN. Allergic bronchopulmonary aspergillosis. *Chest.* 1985;87:81S–84S.

19. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med.* 1977;86:405–414.

20. Greenberger PA. Immunologic aspects of lung diseases and cystic fibrosis. *JAMA.* 1997;278:1924–1930.

21. Greenberger PA, Patterson R. Diagnosis and management of allergic bronchopulmonary aspergillosis. *Ann Allergy.* 1986;56:444–448.

22. Latge JP. *Aspergillus fumigatus* and aspergillosis. *Clin Microbiol Rev.* 1999; 12:310–350.

23. Aubry MC, Fraser R. The role of bronchial biopsy and washing in the diagnosis of allergic bronchopulmonary aspergillosis. *Mod Pathol.* 1998;11:607–611.

24. Kauffman HF. Immunopathogenesis of allergic bronchopulmonary aspergillosis and airway remodeling. *Front Biosci.* 2003;8:e190–e196.

25. Knutsen AP, Bellone C, Kauffman H. Immunopathogenesis of allergic bronchopulmonary aspergillosis in cystic fibrosis. *J Cyst Fibros.* 2002;1:76–89.

26. Chauhan B, Knutsen A, Hutcheson PS, Slavin RG, Bellone CJ. T cell subsets, epitope mapping, and HLA-restriction in patients with allergic bronchopulmonary aspergillosis. *J Clin Invest.* 1996;97:2324–2331.

27. Gondor M, Michaels MG, Finder JD. Non-*Aspergillus* allergic bronchopulmonary mycosis in a pediatric patient with cystic fibrosis. *Pediatrics.* 1998; 102:1480–1482.

28. Akiyama K, Mathison DA, Riker JB, Greenberger PA, Patterson R. Allergic bronchopulmonary candidiasis. *Chest.* 1984;85:699–701.

29. Moreno-Ancillo A, Diaz-Pena JM, Ferrer A, et al. Allergic bronchopulmonary cladosporiosis in a child. *J Allergy Clin Immunol.* 1996;97:714–715.

30. Mroueh S, Spock A. Allergic bronchopulmonary disease caused by *Curvularia* in a child. *Pediatr Pulmonol.* 1992;12:123–126.

31. Lake FR, Froudist JH, McAleer R, Gillon RL, Tribe AE, Thompson PJ. Allergic bronchopulmonary fungal disease caused by *Bipolaris* and *Curvularia*. *Aust N Z J Med.* 1991;21:871–874.

32. Travis WD, Kwon-Chung KJ, Kleiner DE, et al. Unusual aspects of allergic bronchopulmonary fungal disease: report of two cases due to *Curvularia* organisms associated with allergic fungal sinusitis. *Hum Pathol.* 1991;22:1240–1248.

33. Halwig JM, Brueske DA, Greenberger PA, Dreisin RB, Sommers HM. Allergic bronchopulmonary curvulariosis. *Am Rev Respir Dis.* 1985;132:186–188.

34. McAleer R, Kroenert DB, Elder JL, Froudist JH. Allergic bronchopulmonary disease caused by *Curvularia lunata* and *Drechslera hawaiiensis*. *Thorax.* 1981; 36:338–344.

35. Halloran TJ. Allergic bronchopulmonary helminthosporiosis. *Am Rev Respir Dis.* 1983;128:578.

36. Hendrick DJ, Ellithorpe DB, Lyon F, Hattier P, Salvaggio JE. Allergic bronchopulmonary helminthosporiosis. *Am Rev Respir Dis.* 1982;126:935–938.

37. Patterson R, Samuels BS, Phair JJ, Roberts M. Bronchopulmonary torulopsosis. *Int Arch Allergy Appl Immunol.* 1982;69:30–33.

38. Ogawa H, Fujimura M, Tofuku Y. Allergic bronchopulmonary fungal disease caused by *Saccharomyces cerevisiae*. *J Asthma.* 2004;41:223–228.

39. Ikushima S. Case of allergic bronchopulmonary mycosis caused by *Schizophyllum commune*. *Jpn J Antibiot.* 1997;50:47–49; discussion 1997;50:75–76.

40. Tomita K, Hashizume I, Kasamatsu N, et al. Allergic bronchopulmonary mycosis caused by *Schizophyllum commune*. *Nihon Kyobu Shikkan Gakkai Zasshi.* 1996;34:804–809.

41. Matthiesson AM. Allergic bronchopulmonary disease caused by fungi other than Aspergillus. *Thorax.* 1981;36:719.