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Allergic Bronchopulmonary Aspergillosis, Mucoid Impaction of Bronchi, and Bronchocentric Granulomatosis

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Aspergillus fumigatus can give rise to a variety of pulmonary diseases, including immunologic lesions such as asthma, allergic bronchopulmonary aspergillosis (ABPA), and extrinsic allergic alveolitis; to saprophytic reactions such as fungus balls (*i.e.*, mycetomas); and to invasive lesions.[1–3] ABPA can manifest as many pathologic lesions, including mucoid impaction, bronchocentric granulomas, and eosinophilic pneumonia.[4] Each of these pathologic lesions can also be found in diseases unrelated to *Aspergillus* species. ABPA can be viewed as a model for the broader category of allergic bronchopulmonary fungal disease (ABPFD), in which a variety of unusual fungi cause a disease similar to ABPA. The complex associations of these clinical and pathologic entities are discussed in this chapter.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA can be defined as a spectrum of allergic reactions to *Aspergillus* species colonizing the pulmonary airways.[5] The disease was first described in three patients by Hinson and associates in Great Britain, and several large series have subsequently come from that country.[6–9] The first case in the United States was reported in 1968.[10] Patients typically present with pulmonary infiltrates and fevers that are often recurrent, productive cough, brown sputum plugs frequently containing *Aspergillus* organisms, and peripheral blood eosinophilia (>1000/mm^3).

The prevalence of the disease is unknown, in part because the diagnostic clinical and laboratory criteria have evolved over the years. For example, one study from Britain reported that 77% of 143 patients with pulmonary infiltrates and eosinophilia (PIE syndrome) had immediate skin hypersensitivity to *A. fumigatus* antigen, suggestive of ABPA.[7] Using stricter criteria and modern serologic methodology, the frequency of ABPA among asthmatic patients appears to be approximately 6%.[11]

Clinical Features

ABPA often starts in childhood and has a protracted clinical course. It can remain undiagnosed for years, leading to pulmonary fibrosis in the second and third decades of life.[2] Children as young as 2 years of age can be affected, and in one small series of 13 patients, 5 (38%) were younger than 14 years of age; however, ABPA can be seen at any age.[12–14] Patients are typically atopic with a history of asthma that worsens during acute episodes of the disease. In one large series of 111 patients, more than 96% were chronic asthmatics.[7] Tests to exclude ABPA should be part of the

clinical evaluation of all asthmatics, particularly if they have a history of pulmonary infiltrates.[2,11]

Occasionally, asthmatic symptoms are minimal or absent, despite positive sputum cultures and advanced bronchiectasis.[2,5,15,16] Some patients with ABPA have a background of cystic fibrosis.[17–19] Conversely, the incidence of ABPA appears to be markedly increased in patients with cystic fibrosis.[20] Other than symptoms directly attributable to asthma, the most frequent symptoms are fever, cough, and chest pain.[7] Allergic fungal sinusitis with associated symptoms of nasal congestion may accompany the disease.[21] Some patients are entirely asymptomatic. Physical examination of the chest often reveals wheezes and rales. Sputum plugs of different colors are seen in many patients.[2]

The chest x-ray film typically demonstrates infiltrates that correspond to areas of eosinophilic and obstructive pneumonia, mucoid impaction, atelectasis, or fibrosis in late-stage disease (Fig. 63-1). Plain x-ray films can also appear unremarkable. The infiltrates may migrate, but they show a predilection for the upper and middle lobes of lung.[22] ABPA is one of the few diseases (cystic fibrosis is another) that produces proximal cylindrical or saccular bronchiectasis with distal airways of normal caliber.[20] Ring shadows and parallel lines indicative of bronchiectasis are important diagnostic criteria, and they are best shown in linear tomographic studies of the hilar regions.[2,20,22,23] Bronchography may induce exacerbations of asthmatic symptoms and should be avoided.[2,20] The value of thin-section computed tomography scans is not clear. Bronchiectasis can exist even in the absence of demonstrable radiologic infiltrates. Hilar adenopathy is rare.[24]

Laboratory studies play an important role in the diagnosis of ABPA (Display 63-1). Most patients have blood eosinophilia, and many of those with active disease have sputum eosinophilia as well. Patients typically show immediate wheal and erythema in skin tests with *A. fumigatus* antigen, followed by erythema and induration within 4 to 8 hours (*i.e.*, delayed reaction).[11] Serologic studies are useful in the early diagnosis of the disease. In acute episodes, there is an increase in total serum IgE and in serum precipitins to *A. fumigatus*, which typically decline during remission (see Display 63-1).[2,4,25,26]

DISPLAY 63-1. MODERN DIAGNOSTIC CRITERIA FOR ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Major Criteria

Presence or history of infiltrates seen on chest x-ray film

Clinical or radiologic demonstration of proximal (*i.e.*, central) bronchiectasis

Presence or history of asthma

Immediate skin hypersensitivity to *Aspergillus fumigatus*

Serum precipitating antibodies to *A. fumigatus*

Peripheral blood eosinophilia

Elevated total serum IgE (*i.e.*, >1000 ng/mL)

Elevated specific serum polyclonal antibodies (*e.g.*, IgG, IgE, IgA, IgD) to *A. fumigatus* in ELISA studies*

Minor Criteria

Positive sputum culture for *A. fumigatus*

History of expectoration of mucus plugs

Arthus (*i.e.*, late) skin reaction

** Possibly specific for the disease.*
ELISA, enzyme-linked immunoabsorbent assay.
Data from references 11, 20, and 29.

None of these findings are specific for ABPA; each of them can be seen in non-ABPA asthmatics, patients with aspergillomas, and in some patients with cystic fibrosis.[4,20,27,28] However, marked increases in the concentration of serum IgE (*i.e.*, an IgE level >2400 μg/L in patients with cystic fibrosis) in association with other findings are strongly suggestive of ABPA.[20] ABPA characteristically shows polyclonal increases in IgE, IgG, IgD, and IgA directed against *A. fumigatus*, as shown by enzyme-linked immunosorbent assay and other *in vitro* assays.[11,29] These antibody studies appear promising but require more evaluation to determine their sensitivity and specificity. Bronchiectasis often produces sputum plugs, and *Aspergillus* organisms can be cultured from them and in about two thirds of these patients, especially during acute episodes of the disease.[7]

Modern clinical and laboratory criteria for the diagnosis of ABPA are summarized in Display 63-1. Because none of them are deemed pathognomonic, a combination is required for the diagnosis. The presence of six of the major criteria makes the diagnosis probable, and finding seven of them makes it definite.[20] Proximal bronchiectasis is an important key to the diagnosis; patients who have it are said to have ABPA with central bronchiectasis. However, with the use of modern serologic studies, early cases of ABPA without central bronchiectasis can be identified. These patients are said to have seropositive ABPA. Through the use of these clinical and laboratory criteria, lung biopsy can be avoided in most cases.

The natural history of ABPA and factors that lead to progression of the disease are not understood. ABPA can be divided into five clinical stages (Table 63-1).[5,11,22,30] Although this system may be a useful heuristic tool and of value to clinicians in treating

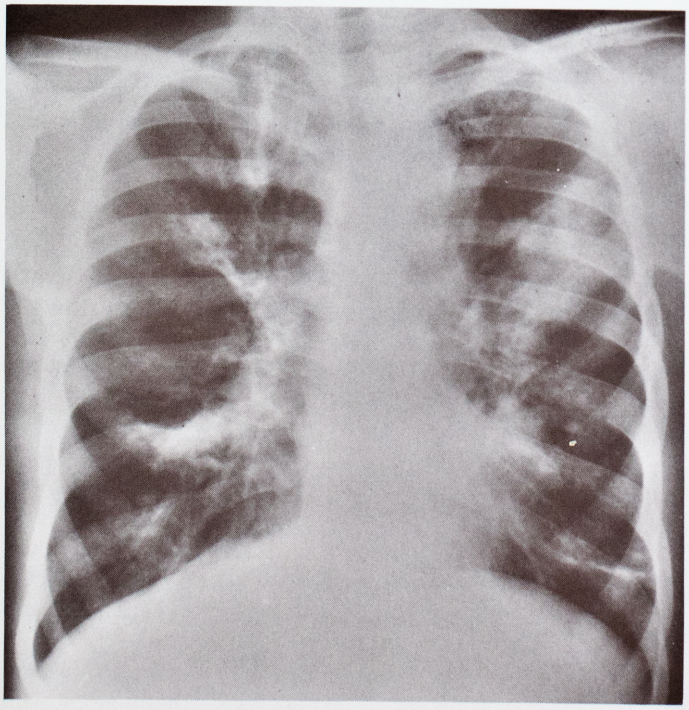

FIGURE 63-1. A posteroanterior chest radiograph of a patient with allergic bronchopulmonary aspergillosis demonstrates dramatic bilateral disease. Abnormal densities radiate from the hilar regions, and Y-shaped branching shadows are seen at the midportion of the lungs.

TABLE 63-1
Clinical Staging System for Patients With Allergic Bronchopulmonary Aspergillosis

Stage	Description
I	Acute disease
II	Remission
III	Exacerbation or recurrence
IV	Corticosteroid-dependent asthma
V	End-stage fibrosis

Data from references 5, 11, 22, and 30.

patients, it implies neither prognosis nor an orderly progression of disease.[30] In one study of 16 patients, only 2 (12.5%) with stage I (*i.e.*, acute disease) progressed to stage V (*i.e.*, pulmonary fibrosis), and patients with exacerbations of disease (*i.e.*, stage III) could return to stage II (*i.e.*, remission) or progress to stage IV (*i.e.*, corticosteroid-dependent asthma).[22] Some patients have developed stage IV disease immediately after presenting with stage I disease.[11] The factors that lead to the development of corticosteroid-dependent asthma or pulmonary fibrosis are unknown.[22] One suggestion has been that high levels of *in vitro* basophil histamine release may correlate with a propensity to advance to stage IV or V.[25]

Treatment of ABPA is aimed at early intervention in the immunologic process with corticosteroids to preclude development of irreversible pulmonary fibrosis.[20,31] This approach can be effective, as shown by the fact that eight patients with stage IV disease treated with low-dose, alternate-day corticosteroids did not show clinical, radiologic, or laboratory evidence of deterioration over a mean course of 10 years.[30]

Pathologic Features

Because the diagnosis of ABPA can be made clinically without a lung biopsy in most cases, there are few detailed pathologic studies of the disease. Available studies indicate that ABPA most prominently affects the airways. Early reports stressed the presence of a polymorphous inflammatory infiltrate in bronchial walls that included numerous eosinophils, lymphocytes, and plasma cells (Figs. 63-2 and 63-3).[6,8,14,32]

In as many as one third of the patients, the larger bronchi are dilated by inspissated, laminated, mucus-containing, degenerated eosinophils and Charcot-Leyden crystals, a histologic picture typical of mucoid impaction (Fig. 63-4).[33] These bronchial plugs often contain scattered degenerated fungal hyphae consistent with *Aspergillus* infection (Fig. 63-5).

Mucoid impaction of smaller, more distal airways (*i.e.*, microimpaction of bronchi) also occurs.[14] Bronchioles contain inspissated mucus and can show intraluminal polyps of fibrous connective tissue (*i.e.*, bronchiolitis obliterans). The distal alveoli sometimes show intraalveolar eosinophils and macrophages typical of eosinophilic pneumonia.[14,32] Marked venulitis has been reported occasionally.[32]

Granulomatous bronchitis and bronchiolitis and necrotizing granulomas associated with eosinophils were sometimes mentioned in older reports but were not considered a hallmark of the disease. However, the study of Bosken and associates based on

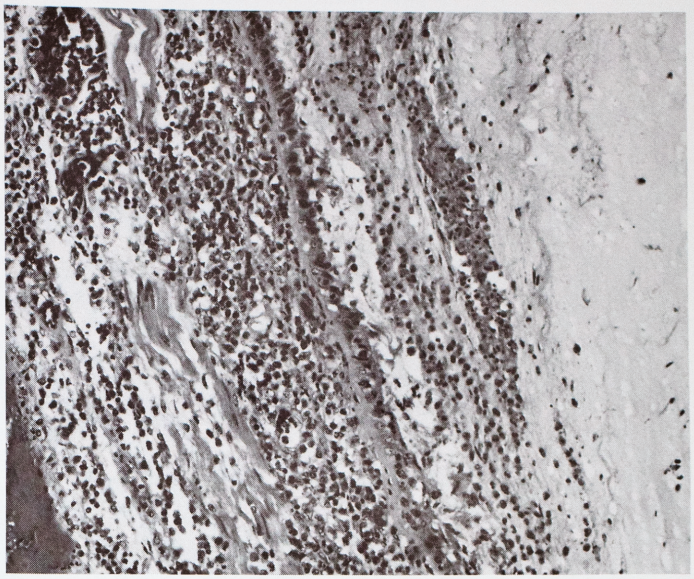

FIGURE 63-2. A microscopic view of the bronchial wall in a patient with allergic bronchopulmonary aspergillosis shows the typical polymorphous inflammatory infiltrate, including numerous eosinophils, lymphocytes, and plasma cells. The bronchial lumen is filled with mucus-containing collections of desquamated respiratory epithelial cells and eosinophils. (H & E stain; low magnification.)

open lung biopsies suggests that necrotizing bronchocentric granulomas typical of bronchocentric granulomatosis are the most common lesion in ABPA, occurring in 10 of 13 cases (77%).[13] Dilated proximal bronchi consistent with mucoid impaction and distal eosinophilic pneumonia were each seen in 62% of the cases, and fungal hyphae were seen in 31% of their biopsies. These results emphasize the spectrum of pathologic lesions that can be found in ABPA and the frequent association with mucoid impaction and bronchocentric granulomatosis. However, bronchocentric granulomas and mucoid impaction of bronchi can be seen in diseases other than ABPA.

Other unusual pathologic features that have been reported in ABPA include aspergilloma and limited tissue fungal invasion into airway walls with formation of peribronchial granulomas.[34–36]

Pathogenesis

The pathogenesis of ABPA is complex and speculative. The elevated levels of specific IgE in serum and the marked tissue eosinophilia suggest participation of type 1 immunity. Although precipitating antibody is found in the serum, immunohistochemical studies for immune complex deposits in lung tissue have shown neither immunoglobulins nor complement.[19] The presence of granulomas and lymphocytic infiltrates consisting of helper and suppressor T cells in lung biopsy specimens suggests a role for cell-mediated immunity, but delayed skin hypersensitivity to *A. fumigatus* has not been reported.[19] One hypothesis is that spores of *A. fumigatus* secondarily colonize the already viscid mucus of patients with asthma or cystic fibrosis, shedding soluble antigens within the mucus that eventually penetrate the bronchial wall. The resulting IgE-mediated mast cell degranulation leads to eosinophil chemotaxis. Helper T cells may react to soluble and insoluble antigens, resulting in a granulomatous response around the airways.[19]

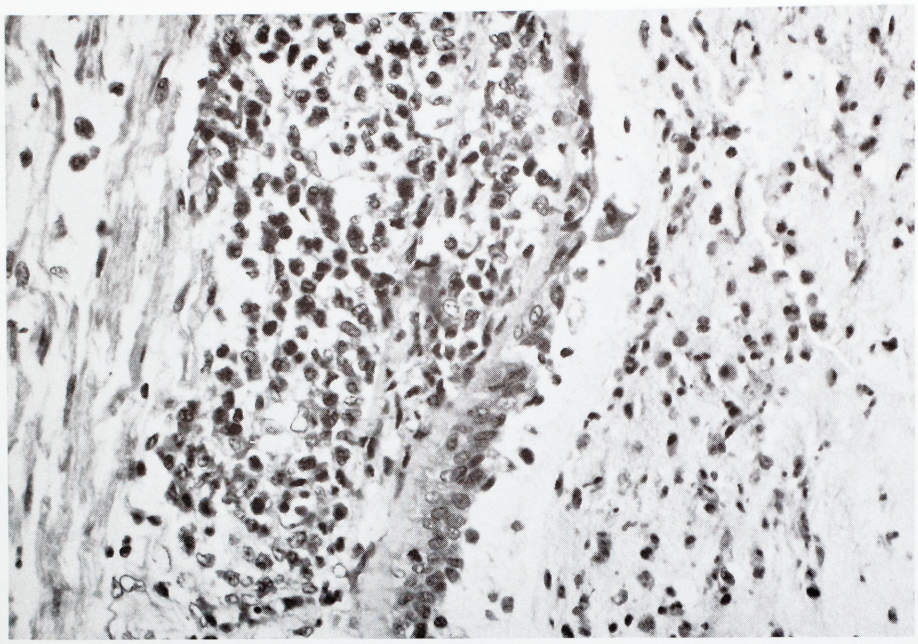

FIGURE 63-3. A microscopic view of the bronchial wall in a patient with allergic bronchopulmonary aspergillosis reveals mixed inflammatory infiltrate in the bronchial wall, partially denuded epithelial surface, and intraluminal mucus-containing eosinophils and desquamated cells. (H & E stain; intermediate magnification.)

Allergic Bronchopulmonary Fungal Disease

Allergy to *A. fumigatus* can be viewed as a paradigm for allergic bronchopulmonary reactions to other fungi (Display 63-2). Virtually all of these fungi are common in the environment and can be laboratory contaminants, but they can also result in diseases such as sinusitis, osteomyelitis, mycetomas, keratitis, meningoencephalitis, and ABPFD.[21,37]

Clinical and laboratory features of these allergic fungal reactions mimic to a greater or lesser extent those of ABPA due to *A. fumigatus*. Many show bronchiectasis, serum precipitins to specific fungi, peripheral blood eosinophilia, and elevated blood serum IgE levels.[11] Some also show bronchocentric granulomatous lesions.[21] Follicular and xanthomatous bronchiolitis have been reported.[21]

As in ABPA, the clinical and immunologic reactions are considered to be a response to fungi, many of which are presumed to have secondarily colonized viscid bronchial mucus. If clinical features suggest ABPA, but there is no clear immunologic or microbiologic evidence of *Aspergillus* organisms, the possibility of an alternate fungus should be considered.[21]

MUCOID IMPACTION OF BRONCHI

Mucoid impaction of the bronchi results from inspissated plugs of mucus within the lumens of proximal segmental and subsegmental bronchi. It is most frequently associated with asthma in the setting of ABPA, but it can be seen in other conditions, such as chronic bronchitis, cystic fibrosis, or obstructing bronchogenic carcinomas.[38] In 1951, Shaw described 10 patients, all of whom had asthma or chronic bronchitis.[39] By 1966, 67 patients had been reported, and by 1975, there were more than 125 patients described in the literature.[14,40]

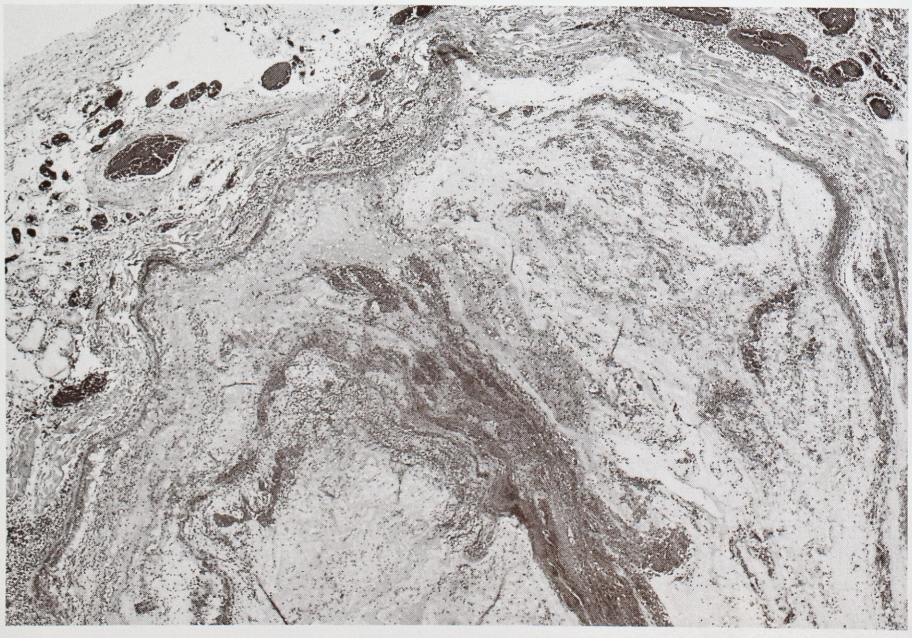

FIGURE 63-4. In a markedly dilated bronchus from a patient with allergic bronchopulmonary aspergillosis, the lumen is filled with mucus. Layers of agglutinated eosinophils impart a laminated appearance to the mucus. (H & E stain; low magnification.)

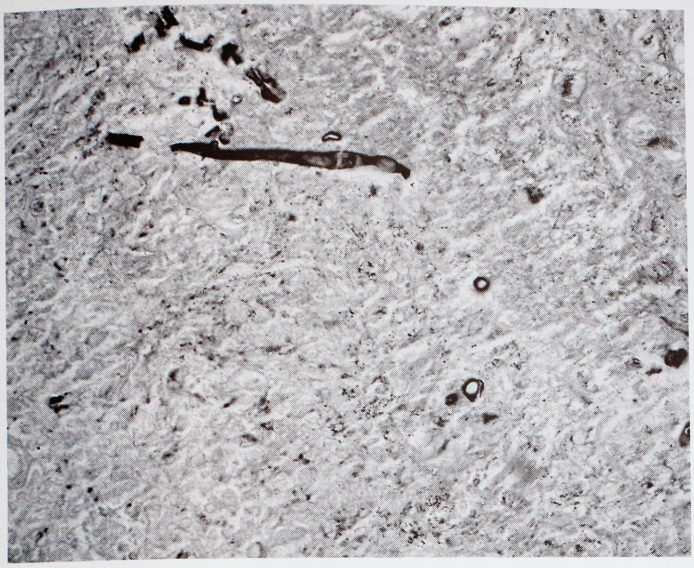

FIGURE 63-5. The mucus in allergic bronchopulmonary aspergillosis has degenerated and fragmented fungal hyphae. (Gomori methenamine silver stain; low magnification.)

Clinical Features

The disease shows neither age nor gender predilections.[14,40,41] Patients have been 4 to 72 years of age at diagnosis. Seventy percent have histories of asthma or chronic bronchitis.[42] The frequency of asthma in different series can vary; for example, Carlson and associates reported asthma in only 1 of 6 patients.[40] Mucoid impaction can also occur in the setting of cystic fibrosis and obstructing bronchial lesions, such as carcinoma, adenoma, and tuberculosis.[38,42,43] Mucoid impaction induced by bronchial lymphangitic metastasis of adenocarcinoma has also been described.[44] Symptoms include repeated respiratory tract infections with a background of fever, productive or nonproductive cough, chest pain, lassitude, weight loss, and hemoptysis.[40,41,45] About 4% to 6% of patients are asymptomatic, and their disease is discovered on routine chest x-ray films.[41,42,45] Patients may give a history of expectoration of rubbery, gray-brown or green mucus plugs.[40] The chest x-ray film features of this disease may be striking and can suggest the correct clinical diagnosis. Several characteristic patterns are caused by the solid mucus plug or plugs within segmental or subsegmental second- to fourth-order bronchi.[40] There can be multiple or solitary oval or rounded lesions that are smoothly outlined. When the nodules are contiguous, a characteristic cluster-of-grapes appearance is seen.[45]

Another distinctive pattern is the presence of V- or Y-shaped shadows with the apex or stem pointed toward the hilum, which occur when the plugs affect bronchi at branch points (see Fig. 63-1).[23,40] Tomograms or computerized axial tomographic scans may help to define these characteristic features. The distal lung can appear normal in mild disease, but it more frequently shows segmental atelectasis or consolidation.[23,40] Rarely, mucoid impaction involves a main stem bronchus, leading to total unilateral atelectasis.[46] Proximal cystic bronchiectasis of the type seen in ABPA may be found.[40] These x-ray abnormalities are most common in the upper lobes, but the lower lobes can also be affected, usually in combination with upper or middle lobes (see Fig. 63-1). Some investigators observe that the chest x-ray film lesions of mucoid impaction can disappear spontaneously, as well as after medical management.[40]

The treatment of mucoid impaction is medical rather than surgical and consists of vigorous therapy with mucolytic drugs and other agents to promote bronchial drainage. If the patient has underlying ABPA, corticosteroids can be used to suppress the manifestations of the disease. Surgical intervention is limited to those cases in which the residua of bronchiectasis or chronic obstruction has resulted in loss of lung function, repeated infections, serious hemoptysis, or other complications.[45]

DISPLAY 63-2. ORGANISMS THAT INDUCE FEATURES MIMICKING ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Candida albicans[65,66]
Curvularia lunata[21,37,67]
Curvularia senegalensis[21]
Bipolaris (as *Dreschlera*) *hawaiiensis*[37]
Bipolaris species (as *Helminthosporium*)[68]
Helminthosporium (?)[69,70]
Stemphylium lanuginosum[71]
Penicillium rubrum[72]
Aspergillus oryzae[73]
Aspergillus ochraceus[74]

Data from references 11 and 21.

Pathologic Features

Several reports have reviewed the pathologic features of mucoid impaction.[14,41,47] The gross specimen is impressive and diagnostic. The impacted mucus, whether intrapulmonary or expectorated, is gelatinous or rubbery, occasionally laminated, and green-yellow, gray, or tan-brown (Fig. 63-6). Within the lung, it fills segmental or sometimes lobar bronchi, which are markedly di-

FIGURE 63-6. Bronchial mucus plugs from a patient with mucoid impaction of the lung show a branching pattern, mimicking the branching of the airways from which they derive.

lated. The impactions are multiple or diffuse in 60% of patients and solitary in the remainder; they can be more than 6 cm long and 2.5 cm wide.[14,41] In most cases, only one lobe is involved, and in almost 70% of patients, it is an upper lobe.[41]

Most cases, especially those associated with allergic reactions to fungi, have a characteristic microscopic appearance. The impacted mucus is laminated, resembling the annual rings of a tree. This pattern is produced by radially arrayed wedges of degenerated or inspissated eosinophils that impart a fir-tree or Christmas tree appearance within the impaction (Fig. 63-7).[47] This pattern of allergic mucin is different from that seen in asthma, in which the eosinophils tend to be arrayed in whorls and eddies.[47] Other findings in the impacted mucus include the Curschmann spirals, Charcot-Leyden crystals, fibrin, and degenerating neutrophils and epithelial cells.[14] In at least 50% of patients, the impaction contains degenerated fungal hyphae consistent with *Aspergillus* sp. or other organisms. They are often visible in hematoxylin and eosin–stained sections, but they may be scattered or sparse. Methenamine silver stains should be routinely performed in cases of suspected mucoid impaction.

The epithelium of the bronchial wall at the impaction site can show squamous metaplasia or erosion. The underlying bronchial wall shows asthmatic changes, such as infiltration by eosinophils and chronic inflammatory cells and thickening of mucosal basement membrane in more than one half of cases. In most cases, the dilated bronchi demonstrate thinning of the walls and atrophy of cartilage.

The lung distal to the impaction is frequently the site of a postobstructive acute and organizing pneumonia, sometimes with abscesses in keeping with bacterial superinfection. Other findings include intraalveolar foamy macrophages typical of obstructive pneumonia, atelectasis, or eosinophilic pneumonia. Eosinophilic pneumonia is seen in about one third of patients and is characterized by intraalveolar aggregates of eosinophils and macrophages.[14,41] Granulomatous pneumonitis or bronchitis—the latter presumably representing bronchocentric granulomatosis—occurs in more than one half of patients.

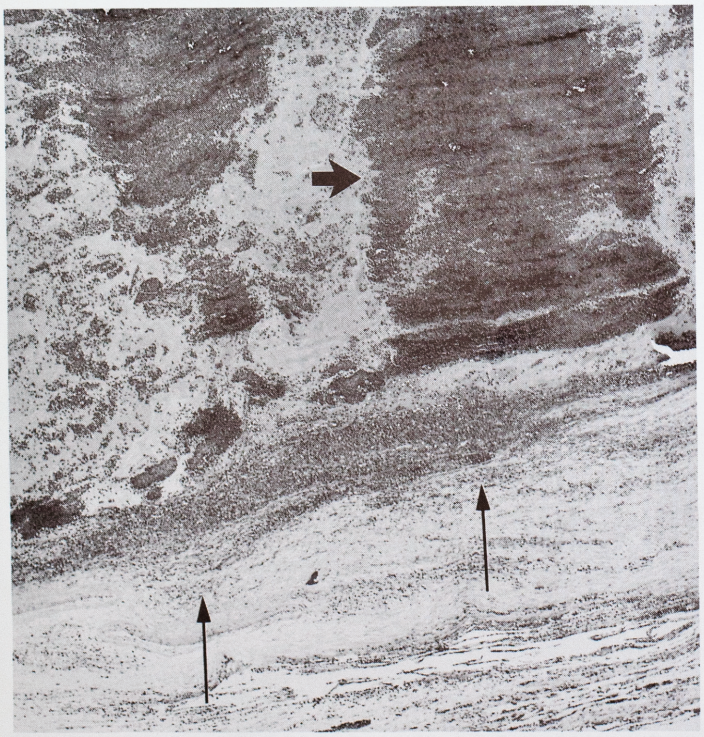

FIGURE 63-7. In a photomicrograph of a bronchus in a patient with mucoid impaction, the radial arrays of degenerated eosinophils (*thick arrow*) impart a Christmas-tree appearance. The attenuated and inflamed bronchial wall is also seen (*thin arrows*). (H & E stain; low magnification.)

Pathogenesis

The pathogenesis of mucoid impaction is still debated. It is probable that most cases are associated with allergic reactions to fungi. At least one half of the cases in early studies had microscopic features of an allergic disorder. Rarely, an asthmatic patient with mucoid impaction may not have laboratory features to support ABPA.[48] Although cases of mucoid impaction have been attributed to cystic fibrosis, allergic aspergillosis can occur in the setting of cystic fibrosis and may be the cause of the mucoid impaction.[14,19]

Although mucoid impaction is reported in other conditions, such as chronic bronchitis, it is unclear whether fungal disease can be entirely excluded in these patients, because many of them were not studied with sophisticated modern serologic assays for *Aspergillus* species or other organisms. Later studies that have looked rigorously for *Aspergillus* organisms in mucoid impaction showed a frequent association with the organism.[47] Conversely, ABPA is frequently complicated by mucoid impaction of large bronchi or microimpaction of smaller airways.[13] Mucoid impaction can occur in the setting of other diseases, such as obstructing carcinoma, but such cases probably lack the features of allergic mucin.

The increased viscosity of the mucin in this disease probably leads to impaction. Early studies speculated that excessive dehydration of secretions, perhaps due to reabsorption of water by the epithelium, or increased DNA content due to inflammation might account for the high viscosity of the mucus.[14] However, other alterations in the chemical composition of the mucin can account for the viscid nature of the mucus. The concentration of glycosaminoglycans per gram of dry weight of mucus in mucoid impaction appears to be higher than that of mucus in patients with chronic bronchitis.[49] Although the mucus in both conditions contains hyaluronic acid as its main constituent, that of mucoid impaction also contains chondroitin sulfate and heparan sulfate or a heparan sulfate–like constituent.[49] The increased concentration of glycosaminoglycans may lead to increased viscosity.

Jelihovsky suggested that, after a central nidus of viscid mucus is in place, the plug grows by new layers of mucus being laid down in apposition to its periphery.[47] The plug eventually distends the bronchus to such an extent that it becomes impossible for it to pass through its orifice.

BRONCHOCENTRIC GRANULOMATOSIS

In 1973, Liebow described a new type of pulmonary granulomatosis defined by the presence of necrotizing granulomas centered on peripheral airways. He called this lesion bronchocentric granulomatosis.[50] Subsequently, he coauthored a comprehensive description of the clinical, radiologic, and pathologic features of the lesion.[14] There have been several small series and several case reports of bronchocentric granulomatosis.[13,47,51,52] From these

studies, it appears that bronchocentric granulomatosis is a distinctive component of ABPA but that bronchocentric granulomas can also occur in rheumatoid arthritis, Wegener granulomatosis, and a variety of pulmonary infections.[13,14,47] Bronchocentric granulomatosis is best considered a descriptive pathologic diagnosis, rather than a single specific disease.

Clinical Features

Cases of bronchocentric granulomatosis can be divided into two groups. Between one third and one half of them occur in the setting of ABPA. As expected, these patients often have asthma.[14,51,52] The asthmatic symptoms frequently begin in childhood, and although the ages at presentation vary from 9 to 71 years of age, many of these patients are in the second and third decades of life.[14] Men outnumber women by 3 to 2. The symptom complex often includes a combination of cough, wheezing, dyspnea, chest pain, and fever, suggesting an exacerbation or recurrence of asthma.[14,52] Laboratory abnormalities include leukocytosis, and in 40% to 90% of patients, peripheral blood eosinophilia. The leukocyte count can reach 25,000/mm^3, although typically the leukocytosis is mild (>10,500/mm^3). Blood eosinophilia ranges from 5% to 69% of the leukocyte count.[14,52] The erythrocyte sedimentation rate is elevated (*i.e.*, 22–120 mm/hour) in all patients tested.

Skin tests for *Aspergillus* antigens may be positive. If positive, the test typically gives a strong immediate response but only a weak delayed response.[53] Serum precipitin titers to *Aspergillus* or *Candida* species are elevated for about one half of these patients.[14] Serum IgE levels, including specific IgE antibody directed against *Aspergillus* species, have been elevated in the few patients tested.[53] Sputum cultures and cultures of the pathologic specimen grow fungi in 20% to 50% of cases.[14,47,52] The fungi recovered are most frequently *A. fumigatus*, but other *Aspergillus* species (*e.g.*, *Aspergillus versicolor*, *Aspergillus niger*) have been reported.[14,47]

Most patients with bronchocentric granulomatosis do not exhibit clinical asthma. These patients tend to be older and are more likely to be female. Although asthmatic symptoms are typically absent, they often have chest symptoms, particularly cough.[14] Other symptoms, such as hemoptysis, pleuritic chest pain, and fever can occur.[51,52] Marked peripheral blood eosinophilia occurs infrequently in this group.[14,52] Sputum or tissue cultures fail to grow *Aspergillus* organisms, and serum precipitin titers for the organism are negative. These patients also have elevated sedimentation rates. There is little difference between asthmatics and nonasthmatics in their radiologic presentation.[14,51–54] A variety of radiologic patterns can be seen, and some patients have more than one type of lesion. Solitary or multiple masses resembling those seen in cancer are found in 20% to 60% of patients. Some of these masses arise from consolidation or atelectasis of segments or lobes of lung.[14] There can also be multiple nodules, a reticulonodular pattern, or pneumonic infiltrates. As many as 10% show a branching pattern of nodular lesions resembling mucoid impaction, and cavitary infiltrates occur in 6% to 27% of the samples.[14,52]

The treatment of patients with bronchocentric granulomatosis depends on whether the disease presents as a localized lesion that can be resected or as more extensive pulmonary infiltrates and on whether it occurs in the setting of ABPA. For patients with localized lesions, surgical excision is often curative. About one third of those who have asthma require treatment with corticosteroids for residual or continuing disease.[14] Most of them improve on this regimen, but some patients continue to have bouts of steroid-dependent asthma.[14] Patients who do not have asthma but who have more diffuse lesions or residual disease after surgery may require treatment with corticosteroids. This treatment results in the clearing of symptoms and radiologic lesions in most cases.[52] The prognosis for patients with bronchocentric granulomatosis is good.[14,51–53] Asthmatic patients do not die of their disease, and only 7% to 13% of nonasthmatics die.[14,51,52] Some of the nonasthmatics had glomerulonephritis at autopsy, and others died as a result of immunosuppressive therapy.[14,27,51] Saldana reported that two of his patients had sinusitis with involvement of the nasal septum.[51] Because bronchocentric variants of Wegener granulomatosis are now recognized and because glomerulonephritis and upper respiratory tract disease are typical findings in Wegener disease, it seems likely that at least some or all of those who died had the bronchocentric form of Wegener granulomatosis.[55] If this is the case, the excellent prognosis of the asthmatic form of bronchocentric granulomatosis can be extended to all cases of the disease.

Pathologic Features

Histologically, bronchocentric granulomatosis shows necrotizing granulomas affecting the small bronchi and bronchioles. The granulomatous inflammation is composed of epithelioid histiocytes arrayed at right angles to the airway lumens and replacing their walls. Because the affected airways are often focally or completely destroyed, it is important to confirm the bronchocentric location of the granulomas. This may be accomplished by showing that the necrotizing granulomas are in continuity with residual bronchial epithelium (Fig. 63-8) or contiguous to pulmonary arteries (Figs. 63-9 and 63-10).

In doubtful cases, elastic stains can be used to demonstrate the residual elastica of the airway or to show clearly the proximity to a pulmonary artery. Larger cartilage-bearing bronchi can have small necrotizing or nonnecrotizing granulomas in their walls and can show severe chondritis, but their mucosal linings are infrequently involved by granulomatous inflammation.[14] Pulmonary arteries show mild inflammation in many cases (see Fig. 63-10). This vasculitis appears to be caused by an overflow from the adjacent bronchial inflammation.[14,52]

Bronchocentric granulomas can be divided into those that show significant tissue eosinophilia and those that do not. The former type is often associated with clinical asthma. The patients have masses of eosinophils, often partially or totally necrotic within the centers of the granulomas and within the lumens of intact airways (see Fig. 63-10). Charcot-Leyden crystals may be seen in the debris. A foreign-body giant cell reaction to the necrotic debris is seen in 40% of the samples (see Fig. 63-9). Cartilage-bearing bronchi show mucoid impaction in 30% to 100% of specimens (see Fig. 63-7).[13,14,47] Jelihovsky suggested that the inspissated eosinophilic debris within these bronchocentric granulomas may be fragments of the mucus plugs formed in larger bronchi, implying that mucoid impaction is a necessary precursor of bronchocentric granulomatosis.[47]

Fungal hyphae can be found in 20% to 90% of samples.[13,14,52] The hyphae often appear dilated and varicose or fragmented, indicating degeneration, and they are noninvasive. They are found more often within proximal bronchial plugs than within the nec-

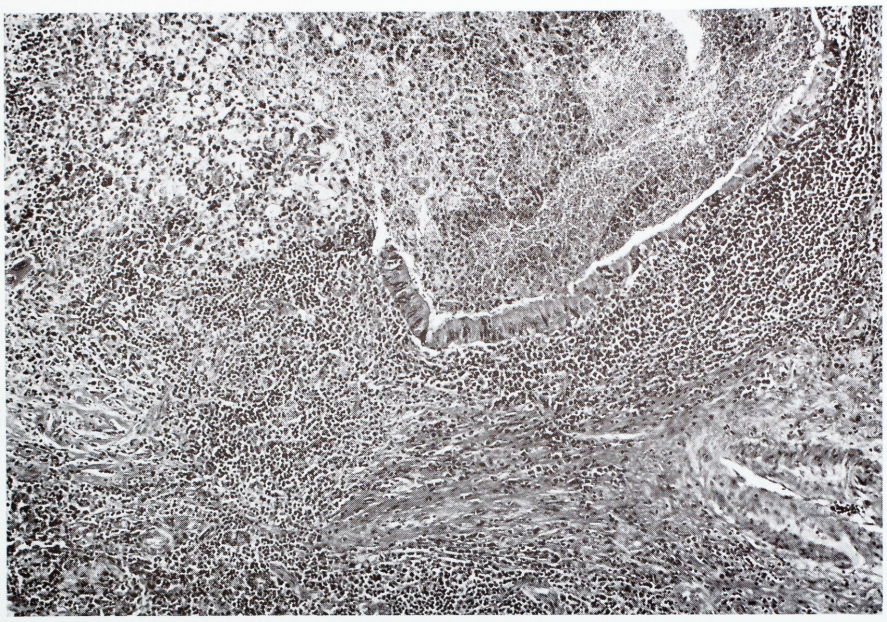

FIGURE 63-8. In bronchocentric granulomatosis, the respiratory epithelium is abruptly destroyed by a xanthogranulomatous inflammatory infiltrate. In other areas, more typical epithelioid granulomas lined the bronchial wall. (H & E stain; low magnification.)

rotizing granulomas of the distal airways.[14,47] They suggest *Aspergillus* species in most cases, but some resemble other fungi such as *Phycomycetes* or *Curvularia* species, and others cannot be classified.[14,21] The fungal hyphae are sometimes surrounded by eosinophilic, radiating, clublike structures typical of the Splendore-Hoeppli phenomenon.[56] These structures are thought to result in part from precipitated antibody protein.

Eosinophils occur within the necrotic granulomas and in the peribronchial tissues. Numerous intraalveolar eosinophils and macrophages suggesting eosinophilic pneumonia can be seen in as many as 20% of of specimens.[14] The second histologic pattern is found principally in nonasthmatics and consists of bronchocentric granulomas containing many neutrophils or acellular necrotic material (Fig. 63-11). Unlike bronchocentric granulomatosis associated with asthma, eosinophils are sparse or absent, and Charcot-Leyden crystals, mucoid impaction of larger bronchi, and eosinophilic pneumonia are not seen. The results of special stains for fungi and bacteria are also negative.

In both types of bronchocentric granulomatosis, certain features are found. There can be intraalveolar foamy macrophages and foci of acute or organizing pneumonia, in keeping with obstructive pneumonia. Interstitial pneumonitis with eosinophils, plasma cells, and lymphocytes can also be seen. Most cases show mild arteritis adjacent to the necrotizing granulomas.

Pathogenesis and Differential Diagnosis

Asthma-associated bronchocentric granulomatosis with tissue eosinophilia appears to be a well-defined clinicopathologic entity that is part of the spectrum of hypersensitivity reactions to fungi, principal among which is *Aspergillus* species. However, other cases of bronchocentric granulomatosis show neutrophilia and fail to demonstrate organisms with the usual special stains. These cases may represent an inflammatory reaction to undetected intrabronchial microorganisms, or they may be a manifestation of other

FIGURE 63-9. Bronchocentric granulomatosis. This necrotizing granuloma completely destroyed the airway, but its bronchocentric location can be identified by its contiguity to a pulmonary artery (*short arrow*). Notice the giant cell (*long arrow*). (H & E stain; low magnification.)

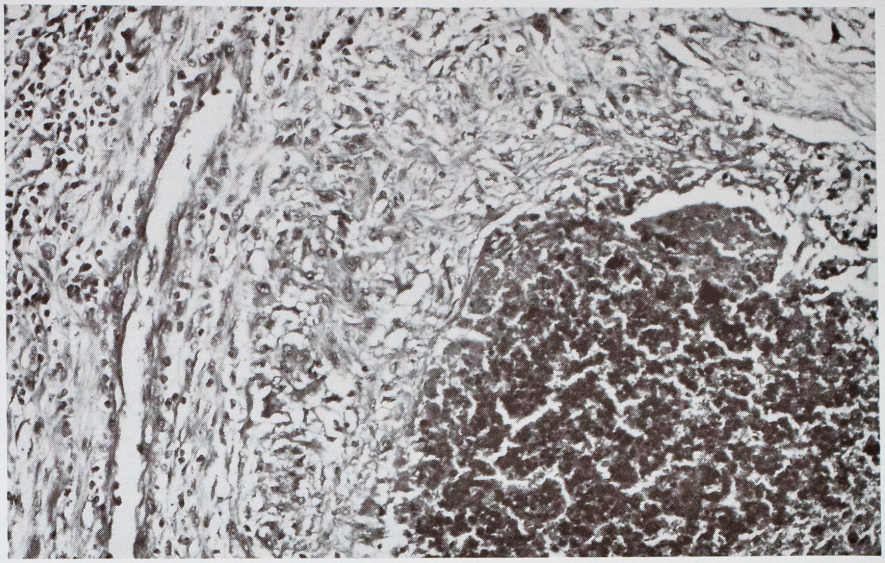

FIGURE 63-10. Bronchocentric granulomatosis with marked tissue eosinophilia. The necrotic debris consists of agglutinated eosinophils lined by epithelioid histiocytes and lymphocytes. The adjoining pulmonary artery shows mild secondary inflammation. (H & E stain; low magnification.)

established diseases, such as rheumatoid arthritis, Wegener granulomatosis, or invasive fungal disease.[52] Bronchocentric granulomas have been found in at least six patients with seropositive or seronegative rheumatoid arthritis.[14,51,57–59] It seems most likely that these bronchocentric granulomas are a manifestation of rheumatoid disease.

We have alluded to the occurrence of a bronchocentric variant of Wegener granulomatosis.[55] This disease usually shows the tissue neutrophilia typical of classic Wegener granulomatosis but may demonstrate moderate tissue eosinophilia. These cases usually show other features that suggest Wegener granulomatosis, such as vasculitis distant from the necrotizing granulomas and extrabronchial necrotizing granulomas. The report of glomerulonephritis and of sinusitis associated with some cases of bronchocentric granulomatosis is in keeping with this unusual variant of Wegener granulomatosis.[14,51] It seems likely that the mortality attributed to bronchocentric granulomatosis may be due to Wegener granulomatosis with a bronchocentric pattern.

Tron and Churg described bronchocentric granulomas in a patient with slowly progressive aspergillosis.[60] This patient did not show asthma or blood or tissue eosinophilia, and there were many fungi present, some of which invaded bronchial walls. Similarly, Tazelaar and associates described fungal-induced bronchocentric granulomas occurring in patients with heart-lung and allogeneic bone marrow transplants.[61] Two of three patients showed tissue invasion. They called these lesions bronchocentric mycosis. Bronchocentric granulomas can occur with more common infectious diseases, such as tuberculosis (27% of patients), blastomycosis, histoplasmosis (8% of patients), and pulmonary echinococcosis. The affected patients are typically nonasthmatic.[62–64]

Bronchocentric granulomatosis, particularly in nonasthmatics, should be diagnosed only if the observer is reasonably certain that the necrotizing granulomas do not involve sites outside of the airways and if the physician can reasonably exclude bronchocentric granulomas of infectious origin or those due to diseases such as rheumatoid arthritis or Wegener granulomatosis. As Myers observed, bronchocentric granulomatosis should be considered a descriptive diagnosis rather than a disease.[63]

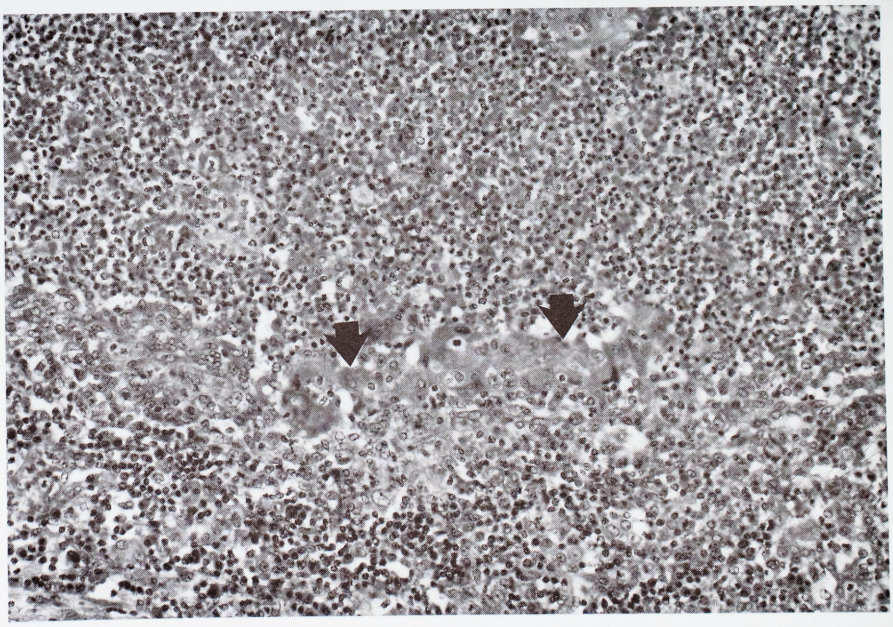

FIGURE 63-11. In bronchocentric granulomatosis, numerous neutrophils are present within the center of the granulomatous inflammation (*arrows*). (H & E stain; low magnification.)

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