

Thoracic aspergillosis (part II)

Primary pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, and related conditions¹

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With the increase in the number of patients receiving immuno-suppressive therapy, the incidence of fungal infection is also on the rise. The fungus *Aspergillus*, a ubiquitous saprophyte, can produce pulmonary as well as systemic infection in several different forms. These include aspergilloma, primary pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, invasive aspergillosis, and disseminated aspergillosis. The manifestations and treatment of these forms of infections vary greatly from one to another. In part II, the authors review and discuss primary pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, and related conditions.

Index terms: Aspergillosis • Fungi • Review articles

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Primary pulmonary aspergillosis is an uncommon disease, which develops when there is a massive inoculum of *Aspergillus* in a normal host without preexisting disease.¹ The possibility of the existence of primary pulmonary aspergillosis was first discussed at the end of the 19th century.² Although Vithayasai et al³ doubt the existence of this form of aspergillosis, many reports have appeared that indicate that primary pulmonary aspergillosis does occur, although rarely.^{2,4–18} According to Teramatsu et al,¹⁹ Tsuibina described 23 cases of primary aspergillosis in the Japanese literature.

PRIMARY PULMONARY ASPERGILLOSIS

Primary pulmonary aspergillosis has been described

in acute and chronic forms.^{4,14,20} In the acute form it is manifested as a pneumonia, with or without abscess formation, and may be fatal.²¹ The chronic form is a granulomatous disease closely resembling pulmonary tuberculosis.²¹ Pulmonary parenchymal involvement is most common, but mediastinal involvement may occur. In 1949, Hertzog et al²² described two cases of primary aspergillosis that developed in a previously healthy five-year-old boy and his 11-year-old sister who lived on a farm. They experienced an acute illness and had diffuse pulmonary infiltrates as shown on radiographs. Both patients died. An autopsy of the boy revealed numerous whitish nodules in both lungs, which on culture grew only *Aspergillus fumigatus*. In 1947, Cawley²⁰ reported a chronic form of primary aspergillosis in a seven-year-old child who, from the age of two weeks, had had recurrent episodes of pneumonia, which were complicated by thoracic wall and cerebellar abscesses from which *A fumigatus* was cultured. Similar cases have been reported by Tobler and Minder²³ in 1954 and Conen et al⁵ in 1962. Hunt et al⁹ described a 24-year-old farmer who had a history of left-sided pulmonary infiltrates, which had been present for seven years. His symptoms included a non-productive cough, progressive dyspnea, and a weight loss of 18 kg (40 lbs). The chest radiograph demonstrated complete opacification of the left lung. The sputum yielded *A fumigatus*, and there was a peripheral blood eosinophilia of 23%. After initial improvement, the patient died. An autopsy revealed extensive involvement of the thoracic organs. Microscopic examination confirmed the presence of *Aspergillus*. Finegold et al¹⁴ described a 60-year-old patient with chronic primary aspergillosis. Mahgoub and El Hassan⁶ reported 3 patients (aged 50, 50, and 45) with primary pulmonary aspergillosis, who had no evidence of other associated diseases. Symptoms included cough with sputum production, hemoptysis (1 patient), weight loss (2 patients), and respiratory distress (1 patient). The chest radiograph of 1 patient revealed a diffuse mottled appearance bilaterally and, in another patient, a left lower lobe opacity. A radiograph was not available in the third case. Two patients died despite therapy with amphotericin B. The third patient, with a left lower lobe opacity, underwent lobectomy and recovered. Gerber et al⁷ reported a 57-year-old patient with dyspnea,

night sweats, and weight loss. The chest radiograph demonstrated infiltrates and cavities in both upper lung fields. He was treated with antituberculosis therapy, without response. Subsequently, he was found to have strongly positive precipitating antibodies and complement fixation titers against *Aspergillus fisherei*. He was given amphotericin B and improved. In a series of 20 cases of pulmonary aspergillosis, Edge et al²⁴ described 2 patients who had no other associated disease. Eastridge et al²¹ found 1 of 55 patients with primary pulmonary aspergillosis. Mediastinal involvement has been reported by Hunt et al,⁹ Cohen and Goggans,²⁵ Puri et al,²⁶ and Ahmad et al.²⁷ The species responsible for mediastinitis in the patient described by Ahmad et al²⁷ was *Aspergillus flavus*; this patient was treated with amphotericin B and 5-fluorocytosine, but died from the sequela of sclerosing mediastinitis.

A fumigatus is the most common organism responsible, but other species have also been isolated.^{6,7,27,28} Although individuals in certain occupations in which there is exposure to materials extensively contaminated with *Aspergillus* spores are thought to be at higher risk, many reports indicate that there may or may not be a history of close or prolonged contact with contaminated material, particularly hay, grains, or straw.^{6,17,27} The disease may occur at any age and has been reported in patients as young as 14 months old¹² and as aged as 74 years old.⁵

Of the patients described in various reports, some had associated conditions such as alcoholism,^{1,8} rheumatic heart disease,²⁹ prior antibiotic therapy,^{4,15,30} psittacosis,³¹ and influenza.^{13,32} It has not been established, however, that these conditions played a role in predisposing these patients to aspergillosis. Fischer and Walker,¹³ who reported primary invasive aspergillosis in a patient who also had influenza, suggested that the viral infection impaired the patient's T-cell function by decreasing the number of T cells in the circulation. However, there are numerous other reports in which no associated conditions were present.^{5-7,10,12,27}

Clinical features

The disease, in its pneumonic form, may be fulminating with a progressive deteriorating course leading to death. There may be dissemination of the fungi to organs other than the lung.

The symptoms are nonspecific and include fever (which may be intermittent), chills, cough (usually nonproductive), dyspnea, pleuritic or diffuse bilateral chest pain, nausea, vomiting, skin rash, and confusion. The symptoms usually are less severe in the chronic form and include low-grade fever, chills, night sweats, weight loss, loss of appetite, and hemoptysis. There may be additional symptoms in patients with mediastinal involvement if superior vena cava syndrome or bronchial obstruction has developed; these include headache, seizures, dysphagia, and dyspnea. The physical examination may reveal diffuse bilateral rales and evidence of consolidation, such as a dull percussion note and bronchial breath sounds.

Diagnosis

Because of its rarity, primary infection with *Aspergillus* may not initially be suspected. Invasive pulmonary aspergillosis should be included in the differential diagnosis of patients with a puzzling, acute pneumonic illness. Factors predisposing to the development of secondary aspergillosis, such as debilitating disease states or physical conditions of the lung, which might facilitate establishment of the fungus, should be excluded. Identifiable radiological features are not typical. The chest radiograph may show a diffuse, fine or coarse, fluffy-edged mottling of both lung fields,^{1,5,8,10,12,29,33} a localized infiltrate,^{5,16,18,26} complete opacification of the lung,⁹ a hilar mass,²⁷ or a combination of cavitary and infiltrative processes^{7,34} (Fig. 1). Radioactive strontium lung scans may be helpful in the diagnosis since it has been observed that this radioisotope concentrates in areas of infection with *Aspergillus*.

Mycology

Sputum examination may demonstrate fungal organisms, but it occasionally may reveal only a few pus cells.⁸ Because of its saprophytic nature and because *A. fumigatus* is recognized most frequently as a contaminant in sputum cultures,⁸ the presence of the fungus does not provide sufficient evidence on which to base a diagnosis of primary pulmonary aspergillosis. However, in view of its pathogenic potential, its possible significance in the sputum should not be ignored,^{8,17} particularly during the evaluation of a pneumonic process. Repeated sputum cultures may be a useful diagnostic aid, but in the case of fulminating disease,

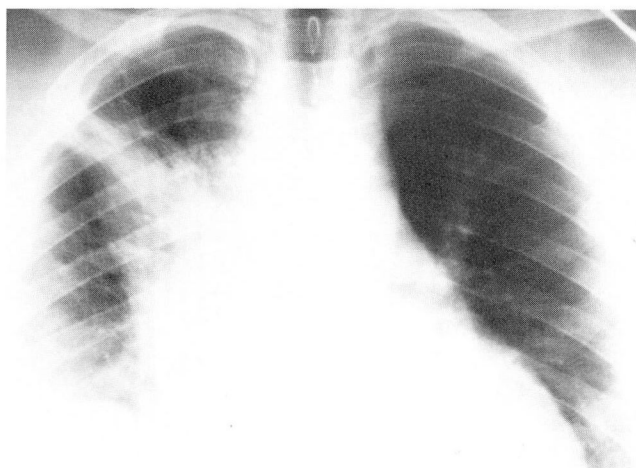


Fig. 1. Primary pulmonary aspergillosis with mediastinal involvement. Note the tracheal narrowing before the bifurcation. The causative organism was *A. flavus*.

the patient may die before these have been obtained. Blood cultures may be negative even in metastatic *Aspergillus* infection.⁸

Immunology

Complement fixation and immune electrophoresis may reveal high complement fixation titers and precipitin bands, but none of these tests alone is proof of active infection. The presence of precipitins should be interpreted with caution since they may be present in 1% to 8% of presumably normal individuals.³⁵ Recently, enzyme-linked immunosorbent assay (ELISA) has been shown to be valuable both for diagnosis and prognosis since increasing titers are a sign of recovery from the disease.³⁶ Estimation of *Aspergillus* antigen by radioimmunoassay has been found to be useful in the early and specific diagnosis of systemic aspergillosis.³⁷ Other laboratory studies, which include complete blood count and erythrocyte sedimentation rate, are nonspecific. The peripheral blood values may vary from an elevated white blood count of 30,000/mm³, with a neutrophil leukocytosis^{9,10} to a normal blood count. There may be lymphopenia,¹³ an increased peripheral eosinophil count,^{9,10} anemia,⁸ and an elevated erythrocyte sedimentation rate.³² Transbronchial biopsy has proved useful in the early diagnosis of aspergillosis.^{32,34} Invasive methods, such as thoracotomy, have been used to establish the diagnosis.^{6,27} It may not be possible

to establish an antemortem diagnosis with non-invasive methods in patients with rapidly progressive disease.

Treatment

Amphotericin B has been used with variable success. However, the results of such therapy are disappointing. Jesiotr²⁸ has reported successful treatment of a patient with primary pulmonary aspergillosis due to *A flavus* with emetine hydrochloride. Successful surgical treatment of a patient with localized disease has been reported by Mahgoub and El Hassan.⁶ In patients with fulminating disease, treatment with amphotericin B rarely is successful, particularly if instituted late. Therefore, the most crucial factor is early diagnosis and initiation of treatment. Surgical resection, if possible, may be the treatment of choice in disease localized to one lobe.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis is characterized by episodes of fever, wheezing, transient pulmonary infiltrates, peripheral blood eosinophilia, and immunological evidence of hypersensitivity to the antigens of *Aspergillus* species. The association between asthma and aspergillosis was first noted, in 1887, by Popoff, as cited by Hinson et al²; but Hinson et al² first described allergic bronchopulmonary aspergillosis in 3 patients who had wheezing, recurrent febrile episodes, radiographic evidence of pulmonary infiltrates, peripheral blood eosinophilia, and sputum plugs containing the fungus. Since that description, the literature related to the clinical pathological features of allergic bronchopulmonary aspergillosis has been abundant.^{3,38-59} Allergic bronchopulmonary aspergillosis usually develops in patients with preexisting asthma, which may or may not be related to fungal allergens.⁶⁰ A personal or familial history of other atopic illnesses is often present.^{30,61} Previously regarded as uncommon in North America, the diagnosis of allergic bronchopulmonary aspergillosis is now being established more frequently.^{3,51,59-72} Because of the increasing recognition of this syndrome, it has become apparent that allergic bronchopulmonary aspergillosis is not an uncommon disorder, but is a significant cause of respiratory disease. Basich et al⁷³ investigated 42 corticosteroid-dependent asthmatics and found 3 with

definite allergic bronchopulmonary aspergillosis and 3 with probable allergic bronchopulmonary aspergillosis. It was suggested that previously undiagnosed allergic bronchopulmonary aspergillosis may be detected in a population of corticosteroid-dependent asthmatics in whom corticosteroids may mask allergic bronchopulmonary aspergillosis and that serial evaluation of such patients may be of value in detecting additional cases of this syndrome. Recently, Patterson et al⁷⁴ observed that corticosteroid-dependent asthma may either precede the diagnosis of allergic bronchopulmonary aspergillosis or may become apparent when an attempt to discontinue corticosteroid therapy is made. Familial occurrence of the disease has been reported by Graves et al⁷⁵; they described two brothers with identical HLA serotypes with allergic bronchopulmonary aspergillosis. The disease has been described in a marijuana smoker by Llamas et al.⁷⁶

The species of *Aspergillus* most commonly associated with allergic bronchopulmonary aspergillosis is *A fumigatus*, but other species, such as *A flavus*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus ochraceus*, and *Aspergillus terreus*, have been implicated.

Although the criteria necessary to establish a diagnosis of allergic bronchopulmonary aspergillosis have been elaborated since they were described by Hinson et al,² a general lack of agreement still exists. Elucidation of the immunological aspects of the syndrome occurred after Pepys et al,³⁰ in 1959, demonstrated type I dermal reaction and precipitating antibodies to *A fumigatus* antigens. In 1958, Henderson³⁹ reviewed clinical, radiographic, and laboratory findings in 22 patients with definite and 10 with probable allergic bronchopulmonary aspergillosis and emphasized the migratory nature of segmental infiltrates in the upper lobes, the presence of precipitating antibodies, and sputum plugs containing fungal hyphae. Radiologically visible mucoid impaction of the large bronchus was present in 8, and saccular bronchiectasis in affected segments in 6. In 1969, Pepys⁴⁷ described additional clinical features and suggested that the type III reaction (Arthus' reaction) requires a preceding type I reaction. In 1971, McCarthy and Pepys^{40,41} reviewed 111 patients with pulmonary eosinophilia and based a diagnosis of allergic bronchopulmonary aspergillosis on transient pulmonary shadows, sputum and blood eosinophilia, and type I and type III skin reactions with *A fumigatus*

extracts. All but 4 of their patients had chronic asthma. Other features considered to be supporting evidence were expectoration of sputum plugs containing fungal mycelium (56%), sputum cultures yielding *A fumigatus* (58%), and bronchograms revealing localized proximal bronchiectasis with normal peripheral bronchi. Patterson et al⁷⁷ observed elevation of serum IgE in allergic bronchopulmonary aspergillosis.

In 1973, Safirstein et al⁵⁷ defined the diagnostic criteria for allergic bronchopulmonary aspergillosis with major and minor divisions. The major criteria consisted of recurrent pulmonary infiltrates shown by chest radiography, blood and sputum eosinophilia, bronchial asthma, and type I and type III skin reactions to *A fumigatus* extracts. The minor criteria included sputum cultures yielding *A fumigatus*, serum precipitating antibodies, a history of plugs in expectorated sputum, and recurrent pneumonia. In a retrospective analysis of 50 patients with allergic bronchopulmonary aspergillosis studied during a period of five years, Safirstein et al⁵⁷ observed that all of the patients fulfilled the major criteria and 33 to 44 patients (66% to 88%) fulfilled the minor criteria. In 1976, Khan et al,⁵⁵ who studied 46 patients with allergic bronchopulmonary aspergillosis, observed that all had episodic airway obstruction and had a skin reaction to *Aspergillus* antigen, 91.1% had pulmonary infiltrates, 80.4% had blood eosinophilia, 91.3% had positive precipitins, and 82.6% had sputum cultures repeatedly positive for *A fumigatus*. These investigators also observed that a multiplicity of precipitin bands corresponded with a higher recovery rate from *A fumigatus*. In 1977, Rosenberg et al⁵³ reviewed 20 patients with allergic bronchopulmonary aspergillosis detected over a period of nine years. They modified Safirstein's criteria and defined them as primary and secondary. Primary criteria included episodic bronchial obstruction, peripheral blood eosinophilia, an immediate skin reaction to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, an elevated serum IgE, a history of transient or fixed pulmonary infiltrates, and central bronchiectasis. Secondary criteria included the presence of *A fumigatus* in the sputum on repeated cultures or under microscopic examination, a history of expectoration of brown plugs or flecks, and a type III reaction to *Aspergillus* antigen. Based on this analysis, the diagnosis of allergic bronchopulmonary aspergillosis was likely if the first six

criteria were present and certain if all seven criteria were present. Ten of 15 patients had positive sputum cultures. Only 1 patient reported expectoration of brown plugs, and a type III reaction was present in only 5 of 15 patients despite the presence of precipitating antibodies in all of these patients. It was suggested that the secondary criteria are not of particular diagnostic value, but that allergic bronchopulmonary aspergillosis should seriously be considered if the sputum cultures are repeatedly positive for *Aspergillus*. In 1977, Malo et al,⁷⁸ who observed patients with chronic allergic bronchopulmonary aspergillosis, found that asthma, episodes of transient pulmonary infiltrates with blood eosinophilia, and type I skin reaction to an extract of *A fumigatus* were present in all 50 patients with chronic allergic bronchopulmonary aspergillosis. However, supporting evidence including the presence of serum precipitins against *A fumigatus* at the time of the study and a history of plugs in the sputum, positive sputum cultures for *A fumigatus*, and chronic radiographic changes were present in only 23 to 44 patients. In 1978, Imbeau et al⁷⁹ established an operational approach for the diagnosis of allergic bronchopulmonary aspergillosis in 40 patients who had been observed for 10 years. This approach suggested that allergic bronchopulmonary aspergillosis should be suspected in patients who present with asthma, pulmonary infiltrates particularly in the upper lobes, eosinophilia, symptoms of pneumonia, or hemoptysis. The diagnosis could be confirmed by positive immediate and late skin reactions to *Aspergillus* antigen, positive serum precipitins, elevated serum IgE levels, positive *Aspergillus* sputum cultures, and demonstration of proximal saccular bronchiectasis on bronchograms. However, it was observed that sputum cultures are not sensitive, corticosteroids may suppress the laboratory abnormalities and the late skin reaction, the variability of *Aspergillus* antigens may produce false-negative results, and that IgE and serum precipitins may revert toward normal several months following an acute episode of allergic bronchopulmonary aspergillosis. In 1979, Wang et al⁸⁰ studied 25 patients with allergic bronchopulmonary aspergillosis. Their criteria (a modification of the criteria of Rosenberg et al⁵³) included asthma, the presence of an immediate wheal and erythema skin reaction to *A fumigatus* antigen, serum precipitins against *A fumigatus* antigen, a serum IgE level more than 2,500 ng/

mL, a history of or radiographic evidence of migratory pulmonary infiltrates, increased IgG and IgE antibody activity against *A fumigatus*, and proximal bronchiectasis as seen on bronchograms. In 1969, Warren and Rose⁷² observed 7 patients with allergic bronchopulmonary aspergillosis. These patients were found to have recurrent pulmonary densities, peripheral blood eosinophilia, purulent sputum yielding *A fumigatus*, precipitating antibodies, and immediate and delayed skin reaction to *A fumigatus* antigen. Malo et al⁸¹ reported that serum IgE levels fall rapidly after the acute episode has terminated.

Pathophysiology

It is unclear whether *Aspergillus* has a special ability to colonize the bronchial tree or merely is trapped in the viscid mucus.^{49,82} However, the changes induced by the preceding immunologic reaction are believed to assist in trapping the fungus, leading to further colonization.⁸³ The primary pathologic process in allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to the fungus present in the bronchial tree. The precise mechanism involved in the pathogenesis is unknown; however, it is likely that a number of immunologic reactions are involved. In 1969, Pepys⁴⁷ suggested that the disease results from a combination of type I and type III hypersensitivity reactions. It was hypothesized that *Aspergillus* sensitizes lung mast cells, which in turn, release mediators, producing bronchospasm, mucous plugs, and submucosal edema as the result of increased capillary permeability. This immediate immunologic reaction is believed to be IgE mediated and probably is responsible for the bronchospastic component, which is the central feature of the disease. A type III immunologic reaction is believed to be responsible for the radiographic changes, which include collapse, consolidation, recurrent pulmonary infiltrates, and bronchiectasis. These changes are thought to occur in response to the diffusion of antigens from fungal mycelia.^{40,41,84} According to Olenchock and Burrell,⁸⁵ the continued presence of the antigens leads to the production of IgG and IgM antibodies, which in turn combine with *Aspergillus* antigen to form antigen-antibody complexes, with fixation of complement at the local site. This localization of immune complexes produces chronic inflammation within the bronchi and peribronchial tissue, resulting in bronchiectasis. Monkey serum transfer studies by Golbert

and Patterson⁴⁹ support this postulate. Recent studies by Slavin et al⁸⁶ confirm the important mechanism of immune complex formation and complement deposition at the local level. Marx and Flaherty⁸⁷ suggested that IgA at the local site may play a role in tissue destruction through activation of the alternate complement pathway. Geha⁸⁸ and Dorval et al⁸⁹ detected the presence of circulating immune complexes. Chan-Yeung et al⁵⁰ described necrotic granulomas in 2 and partial granulomas dissection in 1 of 3 patients. They attributed these abnormalities to a type IV cell-mediated reaction. Recently, Rosenberg et al⁵³ demonstrated in vitro lymphocyte transformation to *Aspergillus* antigen in patients with allergic bronchopulmonary aspergillosis, but did not believe that this could be used diagnostically. Patterson et al⁹⁰ suggested three possible mechanisms for the immunological reactions in allergic bronchopulmonary aspergillosis: (a) a nonspecific IgE stimulating factor produced by *Aspergillus*-sensitized T cells that could be responsible for the marked IgE response observed in allergic bronchopulmonary aspergillosis, (b) *Aspergillus* antigen that could inhibit T suppressor cells for IgE producing B lymphocytes, and (c) the simultaneous presence of antigen and antibody within the bronchi. Parker et al⁹¹ suggested that antigen antibody complexes might convert null cells into cytotoxic killer cells, which in turn, could destroy antibody-coated target cells. Flaherty et al⁹² were unable to discover an increased frequency of specific HLA antigens in 20 patients with allergic bronchopulmonary aspergillosis.

Pathologic findings include dilated bronchi filled with inspissated mucus and exudates, in which noninvasive fungal hyphae may be identified.^{2,93,94} Squamous metaplasia of the bronchial mucosa and bronchial wall and infiltrates consisting of eosinophils, plasma cells, and lymphocytes may be present.^{40,41} Golbert and Patterson⁴⁹ reported focal eosinophilia and bronchiolitis obliterans. Tissue invasion by the fungus has been described, but is uncommon,^{39,56,95} and Riley et al⁵⁶ have suggested that invasion may be related to corticosteroid therapy. Aspergilloma is a rare complication.^{39,95,96} Allergic bronchopulmonary aspergillosis is only one of the possible clinical presentations of allergy to *Aspergillus*. Others include mucoid impaction, eosinophilic pneumonia, and bronchocentric granulomatosis. Katzenstein et al,⁹⁷ in a review of pathological data of patients with allergic bronchopulmonary asper-

gillosis, discovered overlap between these clinical entities.

Clinical features

There is no age or sex predominance. The illness has a wide variety of clinical manifestations that depend on the severity of the disease. Patients frequently present with fever, productive cough (often with blood-streaked sputum), intractable asthma, weight loss, chest pain, and general malaise simulating a flu-like syndrome.⁹⁸ The disease in its mild form may be confused with extrinsic asthma, resolving without any treatment.

McCarthy et al⁹⁹ noted that in the presence of minimal asthmatic symptoms, the radiograph may show consolidation, and when this has resolved, the disease may be suspected on the basis of the residual pulmonary damage. Safirstein et al⁵⁷ stated that some patients may remain asymptomatic, while the chest radiograph demonstrates pulmonary infiltrates. McCarthy and Pepys,^{40,41} who evaluated 111 patients with allergic bronchopulmonary aspergillosis, reported that 56% of the patients had intermittent and 44% had continuous sputum production. The sputum revealed plugs in 54%, 84% of whom had mucopurulent sputum. There was no relation between asthma and the presence of sputum plugs. Febrile episodes developed in 68% of patients; these episodes lasted from one half hour to many hours or days. Blood-streaked sputum was present in 80% of the patients. Four patients had severe hemoptysis. Hemoptysis followed episodes of pulmonary eosinophilia in 39 patients. Chest pain was present in 61 patients (55%); it was pleuritic in 44 patients and was localized to the side involved according to chest radiography. Of 32 patients studied by Henderson,³⁹ 4 had a history of expectoration of plugs, 11 had experienced mild hemoptysis, 18 had had an intermittent productive cough, 11 had had pyrexia with one or more episodes of pulmonary infiltration, and 1 had had pleuritic chest pain. Safirstein et al,⁵⁷ who studied 50 patients, observed hemoptysis in 40% and sputum plugs in 66%. Radha and Viswanathan¹⁰⁰ studied 17 patients with allergic bronchopulmonary aspergillosis and found a 47% incidence of hemoptysis, a 67.6% incidence of sputum plugs, and a 94.3% incidence of cough. In 46 patients studied by Khan et al,⁵⁵ hemoptysis was present in 23, sputum plugs in 30, and febrile episodes in 29. Wheezing was present on physical

examination in virtually all patients. Crepitant rales may be present; these are localized in the areas of pulmonary infiltrates or areas irreversibly damaged by the disease. In one study, rales were present in the upper lung zones in 75% of patients.^{40,41} Clubbing of the fingers also may be present.^{40,41} Nasal plugs, similar to those expectorated from the bronchi, have been reported in 10% of patients.^{40,41} Upper airway obstruction may be the only presenting symptom in some patients with allergic bronchopulmonary aspergillosis. Safirstein¹⁰¹ described a 24-year-old woman with allergic bronchopulmonary aspergillosis whose symptoms were recurrent nasal obstruction, mucosal ulceration, edema, and thick secretions within the nose. Exacerbations of the disease in the winter and spring months in Britain have been attributed to high atmospheric *Aspergillus* spore counts during these months.^{57,102-106}

Radiographic features

Although Hinson et al,² in 1952, described some of the radiographic features of allergic bronchopulmonary aspergillosis, it was not until 1970 that they were described in detail by McCarthy et al.⁹⁹ Their description of radiological abnormalities in 111 patients included:

1. Massive homogeneous shadows, including patchy densities in 83 patients, lobar consolidation in 30 patients, circular infiltrates in 26 patients, V-shaped ("gloved finger") infiltrates in 11 patients, oblong (2 cm in length) infiltrates in 22 patients, triangular infiltrates in 51 patients, and irregular infiltrates in 15 patients. Infiltrates of smaller size were often of low density.
2. "Tramline" shadows (two parallel hairline shadows extending out from the hilum in the direction of the bronchi) in 23 patients. The lines probably represent edema in the normal bronchial wall. These were common, transient, and most frequently observed in patients less than 15 years old.
3. Parallel line shadows in 77 patients; these shadows are similar to tramline shadows, but the transradiant zone is wider than that seen in the normal bronchus, indicating that these bronchi are dilated.
4. Bandlike shadows ("toothpaste"-like shadows) in 37 patients. The bandlike shadow is 2-3 cm long, 5-8 mm wide, and represents secretions in a dilated bronchus. In some patients, toothpaste shadows alternated with parallel shadows;

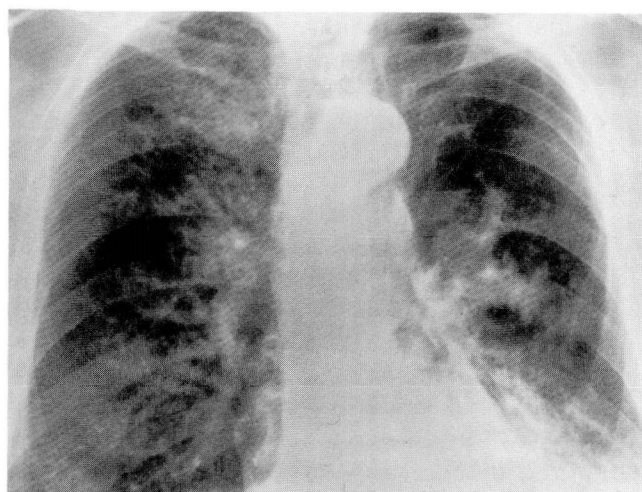


Fig. 2. Allergic bronchopulmonary aspergillosis. The gloved-finger-shaped infiltrate can be seen in the left hilar region.

this was noted after the patient had expectorated sputum plugs. Occasionally, two such shadows formed a V-shaped or Y-shaped shadow after joining at an acute angle.

5. Gloved-finger shadows in 11 patients. These shadows were seen as bandlike shadows, with an expanded, rounded end, and are produced by secretions in a dilated bronchus with an occluded distal end. These shadows disappeared after the patient had expectorated sputum (Fig. 2).

6. Ring shadows in 51 patients. These configurations are described as end-on shadows of dilated bronchi. Their size varied from 5–8 mm (“honeycomb” shadows) to 1–2 cm. A transient fluid level was seen in some of these shadows, while in others, a circular shadow was formed after they had become filled with secretions.

7. Line shadows in 36 patients. These shadows are thought to represent the wall of a bulla in some patients and indrawn pleura in others.

Other abnormalities included: nodular shadows (27 patients) seen only in association with other shadows; atelectasis of a lobe or entire lung (12 patients) due to occlusion of a bronchus by a plug of mucus and fungus; permanent lobar shrinkage (31 patients) with underlying bronchiectasis, usually bilateral and most common in the upper lobes; local emphysema, indicated by increased transradiancy with either no vessels or narrow vessels shown on the initial radiograph (11 patients) and on the final radiograph (28 patients). A mixture of different types of shadows

was observed in some cases. The incidence of radiographic changes in the upper lobes was high. Mintzer et al,⁷⁰ who investigated 20 patients, observed perihilar pseudoadenopathy in 8 and air-fluid levels in 4 patients, in addition to the findings described by McCarthy et al.⁹⁹ Mintzer et al⁷⁰ concluded that these additional findings were due to dilated perihilar bronchi filled with fluid. Malo et al¹⁰⁷ reviewed 1,242 radiographs in 50 patients followed for two to 25 years (mean, 10.9 years). These investigators found changes similar to those described by McCarthy et al,⁹⁹ except that consolidation was equally distributed in all lung zones, as compared to upper lobes in most of the patients studied by McCarthy et al. Asymptomatic acute episodes, leading to a delay in obtaining a chest radiograph, have been reported by many investigators.^{69,99,107} Scadding¹⁰⁸ described circular proximal bronchiectasis as shown on bronchograms. Rosenberg et al⁵³ suggested that this finding may be used as confirmation of allergic bronchopulmonary aspergillosis if other clinical and immunological criteria are present. Menon and Das,¹⁰⁹ who studied 500 radiographs of 50 patients for five years, described other features. These included (a) empty or full “wine-glass” shadows, depending on the presence of bronchial secretions in these dilated obstructed bronchi, attributed to dilatation of medium-sized bronchi obstructed with mucous plugs; (b) “gossamer” shadows, described as shadows appearing like spiderwebs or a thin muslin veil, because of irregular dilatation of the bronchi; and (c) “lotuslike” shadows, described as homogeneous shadows resembling a half-opened lotus, because of irregular dilatation of the bronchi. Rosenberg et al¹¹⁰ described 3 patients with allergic bronchopulmonary aspergillosis with normal chest radiographs; the diagnosis was confirmed by the demonstration of proximal bronchiectasis on bronchograms.

Immunology

Pepys et al,³⁰ in 1959, were first to describe the presence of precipitating antibodies to *Aspergillus* extract in the serum of patients with allergic bronchopulmonary aspergillosis. In 1971, McCarthy and Pepys,^{40,41} using the agar gel method for precipitins to *A fumigatus* in 99 patients, demonstrated a positive reaction in unconcentrated serum of 71 patients. Additional tests of 16 of the negative sera, after threefold to fourfold concentration, yielded further positive reactions

in nine, increased the sensitivity in unconcentrated serum from 72% to 92%. Malo et al,⁸¹ investigating 50 patients with a double gel immunodiffusion method, demonstrated a 20% increase in serum precipitin positivity after concentration. Another method used to estimate serum precipitins is counterimmune electrophoresis. This technique is more sensitive than the double diffusion method when dealing with unconcentrated serum, but less sensitive when serum is concentrated. The detection of serum precipitins must, however, be interpreted with caution, since they may be present in 1% to 8% of presumably normal individuals^{35,111} and in 7% to 12% of patients with asthma who have no manifestations of allergic bronchopulmonary aspergillosis.^{35,42,51}

The serum IgE is moderately elevated. The serum IgG may be either slightly increased or normal. The serum IgM usually is normal.^{53,112,113} The serum IgG has been found to be elevated in approximately 40% of patients.^{113,114} Patterson et al,⁷⁷ in 1973, first reported the association between elevated serum IgE levels and allergic bronchopulmonary aspergillosis. Rosenberg et al,⁵³ in a study of 20 patients, detected concentrations of serum IgE ranging from 644 to 6,400 ng/mL. The major component portion of serum IgE is nonspecific and is not directed against *Aspergillus*. The ratio between specific and nonspecific IgE is approximately 5%.^{90,115} Elevated IgE levels are nonspecific in allergic bronchopulmonary aspergillosis and may be present in patients with other pulmonary diseases, particularly extrinsic asthma.¹¹⁶ Pauwels et al¹¹⁷ investigated 143 patients with different forms of bronchopulmonary aspergillosis and noted elevated total serum IgE levels not only in allergic bronchopulmonary aspergillosis, but also in other forms of the disease. Specific IgE antibodies to *A fumigatus* were found primarily in patients with allergic bronchopulmonary aspergillosis. Specific antibodies, consisting predominantly of the IgG and IgM class of immunoglobulins, have been found to be elevated in most patients with allergic bronchopulmonary aspergillosis.^{53,116,118} Cytophilic serum antibodies, belonging to the IgG subclass, also have been observed in patients with allergic bronchopulmonary aspergillosis.⁴⁸ In a recent report, Patterson et al⁷⁴ suggested that specific IgE and IgG antibodies directed against *Aspergillus* antigen are helpful not only in the diagnosis of allergic bronchopulmonary aspergillosis in its acute

stage, but also when the patient is being treated with corticosteroids or has a chronic (fibrotic) disease. Assem and Turner-Warwick⁴⁸ suggested that the type I immediate skin or bronchial reaction observed in patients with allergic bronchopulmonary aspergillosis may be mediated by IgG-4, in addition to IgE. Lymphocyte blast transformation has been observed by some investigators. Of 5 patients with allergic bronchopulmonary aspergillosis investigated by Forman et al,¹¹⁹ 3 were found to have significantly elevated lymphocyte blast transformation against *Aspergillus* antigen. Rosenberg et al¹²⁰ also noted increased lymphocyte blast transformation in their patients, but stated that serial changes in this test do not correlate with activity of the disease. McCarthy and Pepys^{40,41} detected bacterial precipitins, particularly to *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*, in 60% of patients. These investigators also demonstrated immediate and delayed nasal and bronchial responses when patients were challenged with *Aspergillus* antigen.

Skin testing

According to Ciszek,¹²¹ skin testing to establish the diagnosis of aspergillosis was first used by Macaigne and Nicaud, in 1927, who obtained positive reactions in two cases of pulmonary aspergillosis, and Pasteur et al, in 1928, who tested 4 patients with aspergillosis, all of whom had positive skin reactions of the immediate and delayed type. Pepys et al³⁰ investigated 27 patients with *A fumigatus* in the sputum. Sixteen of the 27 patients had a positive skin test with *Aspergillus* extract and had episodes of pulmonary eosinophilia. Eleven patients who had no episodes of pulmonary eosinophilia had infrequent reactions to the skin-test material. In addition to immediate wheal reactions, late reactions of the Arthus type appeared in a number of patients. Of 111 patients with allergic bronchopulmonary aspergillosis tested by McCarthy and Pepys,^{40,41} all had positive skin tests (type I reaction) to *A fumigatus* and 92 demonstrated a positive reaction to *A terreus*. The type III reaction was observed three to five hours after the peak test in 16%. Hoehne et al,⁵¹ who studied 14 patients, found a positive dual reaction in 4% of apparently normal individuals and in 36% of allergic asthmatics without evidence of allergic bronchopulmonary aspergillosis. Thirty-eight percent of asthmatics and 14% of patients with pulmonary disease, other than

allergic bronchopulmonary aspergillosis, demonstrated positive type I reactions in another study.³⁵ Louridas¹²² detected a 20% (70 patients) incidence of immediate reaction and a 7.8% (27 patients) incidence of dual reaction in 344 patients with chronic pulmonary disease. Of the 70 patients with a positive immediate skin reaction, 10 had no evidence of any form of aspergillosis. Louridas also found that 24% (130 patients) of 534 asthmatics and 4.5% (11 patients) of 242 normal individuals had positive immediate skin reactions. Similar results have been reported by other investigators.^{42,98} Slavin and Winzenburger¹²³ in an atopic patient population of 379 individuals, observed a 17% incidence of positive immediate skin reactions. Longbottom et al¹²⁴ observed a 50% incidence of positive immediate skin reaction in asthmatics. Rosenberg et al⁵³ and Novey and Wells⁶⁷ reported a 33% and 81% incidence of positive dual skin reactions, respectively. These reports indicate that positive skin reactions are not highly specific for allergic bronchopulmonary aspergillosis and should be interpreted with caution.

Mycology

Sputum cultures were positive for *Aspergillus* in 58% in one series.^{40,41} Henderson³⁹ reported positive sputum cultures in 31 of 32 patients with allergic bronchopulmonary aspergillosis. Of 50 patients studied by Safirstein et al,⁵⁷ 19 had sputum cultures positive for *A. fumigatus*. In one series, 24% of asthmatics and 6% of individuals with other pulmonary diseases were found to have sputum cultures positive for *Aspergillus*.⁴² Rosenberg et al⁵³ reported that two thirds of patients had positive sputum cultures. Multiple positive sputum cultures may suggest the presence of allergic bronchopulmonary aspergillosis, but, because of the ubiquitous nature of *Aspergillus* and its potential for being a laboratory contaminant, this evidence alone usually is considered a poor diagnostic indicator.

Pulmonary function studies

Abnormal pulmonary function in patients with allergic bronchopulmonary aspergillosis has been reported by many investigators.^{40,41,57,78} Malo et al,⁷⁸ evaluating 50 patients with allergic bronchopulmonary aspergillosis, observed a normal FEV₁ in 12 and an FEV₁ reduced to levels less than 45% in 12 other patients. Patients with reduced

FEV₁ had severe airway obstruction. Similarly, the vital capacity was reduced in 20 patients and the diffusing capacity below 75% in 9 patients. Functional residual capacity was reduced in 4 patients, normal in 23, and increased in 23. Nineteen patients had airway obstruction, with reduced FEV₁, hyperinflation, and an increased functional residual capacity; airway resistance was increased in 17 patients. Reversibility of airway obstruction with bronchodilators, indicated by a 15% or greater change in FEV₁, was observed in 17 patients. In another study, a normal diffusing capacity and airway obstruction with less reversibility after isoproterenol inhalation has been observed.⁵⁷ Of 86 patients investigated by McCarthy and Pepys,^{40,41} most had reduced FEV₁ and FVC, and the FEV₁/FVC ratio was less than 70%. Reversibility in airway obstruction with isoproterenol inhalation was limited, particularly in those with FEV₁ measurements of about 35% of the predicted value. Twenty-six patients had less than a 10% improvement in airway obstruction. Diffusing capacity was reduced in most of the patients. Malo et al⁷⁸ suggested that the impairment in diffusion capacity correlates with the duration of the disease in such patients and may be used to assess the severity of allergic bronchopulmonary aspergillosis.

Patterson et al,⁷⁴ in a recent report, divided allergic bronchopulmonary aspergillosis into five stages:

1. The acute stage, when the patient demonstrates all of the classical symptoms and laboratory findings.

2. Remission, when after treatment of the acute stage, there is a clearing of pulmonary lesions, a decline in total serum IgE levels, and the patient remains in remission following discontinuation of corticosteroid therapy (usually after six months).

3. Exacerbation, when the patient either has recurrence of the disease with all of the characteristic acute clinical features or has asymptomatic disease in which there is a greater than twofold rise in the serum IgE, and radiographic evidence of asymptomatic pulmonary shadows.

4. Corticosteroid-dependent asthma. Corticosteroid therapy cannot be discontinued without the recurrence of severe asthma. This stage sometimes may precede the diagnosis of allergic bronchopulmonary aspergillosis. There is no sex predilection in this stage. It develops in young patients, and there are positive precipitins, elevated specific IgE and IgG, and elevated mean

total serum IgE levels despite continued corticosteroid therapy.

5. The fibrotic stage. This develops in patients with long-standing allergic bronchopulmonary aspergillosis. Such patients have obstructive lung disease and fibrotic changes that can be demonstrated by radiography and at autopsy. Additionally, there may be a reversible bronchospastic component that requires corticosteroid therapy. The total serum IgE and specific IgG remain elevated in most cases despite corticosteroid therapy.

There is no universal agreement among investigators concerning what criteria are required to establish a diagnosis of allergic bronchopulmonary aspergillosis. Bardana⁹⁸ recently has proposed a comprehensive list of criteria for diagnosis (*Table 1*): The diagnosis of allergic bronchopulmonary aspergillosis is considered definite if, in addition to the first four criteria, at least three of the last four criteria are present. The diagnosis is considered probable if, in addition to the first three criteria, at least four of the last five criteria are present or are clearly documented by medical records. The diagnosis is considered possible if, in addition to the first two criteria, at least three of the last six criteria are present or are clearly documented by medical records. Bardana⁹⁸ suggested that the presence of documented aspergillosis, cystic fibrosis, long-standing non-*Aspergillus*-induced pulmonary disorders, chronic granulomatous disease of childhood, congenital or variable acquired hypogammaglobulinemia, parasitic infection, tropical eosinophilia, or periarthritis nodosa excludes the diagnosis of allergic bronchopulmonary aspergillosis.

Diagnosis

Most patients with allergic bronchopulmonary aspergillosis present with recurrent pulmonary infiltrates and bronchospasm. If such patients additionally have a history of expectoration of sputum plugs, elevated peripheral blood eosinophil counts, and sputum cultures positive for *Aspergillus*, allergic bronchopulmonary aspergillosis must be suspected. Such patients should be further investigated with skin tests for *Aspergillus* sensitivity and a determination of serum IgE and serum precipitins. Specific anti-*Aspergillus* IgG or IgE may be used to further support the diagnosis. Bronchography may be employed if the diagnosis is still in doubt.

Diagnosis during the fibrotic stage, as described by Patterson et al,⁷⁴ depends on a history

Table 1. Diagnostic criteria for allergic bronchopulmonary aspergillosis

Bronchial asthma
Type I cutaneous reactivity to <i>Aspergillus</i> extract
Total serum IgE levels >2,500 ng/mL
Two of the following radiographic findings: -Transient or fixed pulmonary infiltrates -Mucoid impaction -Bilateral upper lobe contraction with or without fibrotic changes -Beaded central bronchiectasis with normal peripheral tapering
One or both of the following: -Fever -Weight loss
Three or more of the following: -Productive cough -Hemoptysis -Expectoration of brown plugs -Positive sputum culture for <i>Aspergillus</i> -Documented recurrent pneumonia
Peripheral blood eosinophilia (absolute count >500/mm ³)
-Demonstrable precipitating antibody to <i>Aspergillus</i> antigens in unconcentrated sera
-Quantitative increase in total anti- <i>Aspergillus</i> antibody or specific anti- <i>Aspergillus</i> IgG or specific IgE

Table 2. Differential diagnosis of ABPA

Tuberculosis (upper lobe involvement)
Cystic fibrosis (many common features)
Mucoid infection
Bronchocentric granulomatosis
Extrinsic allergic alveolitis
Other causes for eosinophilic pneumonia - Helminthic infections <i>Ascaris duodenale</i> - Trichinosis - Filariasis - Cutaneous and visceral larva migrans - Strongyloidiasis - Schistosomiasis - Dirofilariasis - Drugs - Penicillin - Hydralazine - Para-aminosalicylic acid - Nitrofurantoin - Chlorpropamide - Mecamylamine

of asthma, the presence of fibrosis, a suspicion of allergic bronchopulmonary aspergillosis, demonstration of central bronchiectasis, and findings of elevated specific IgG, IgE, and total serum IgE.

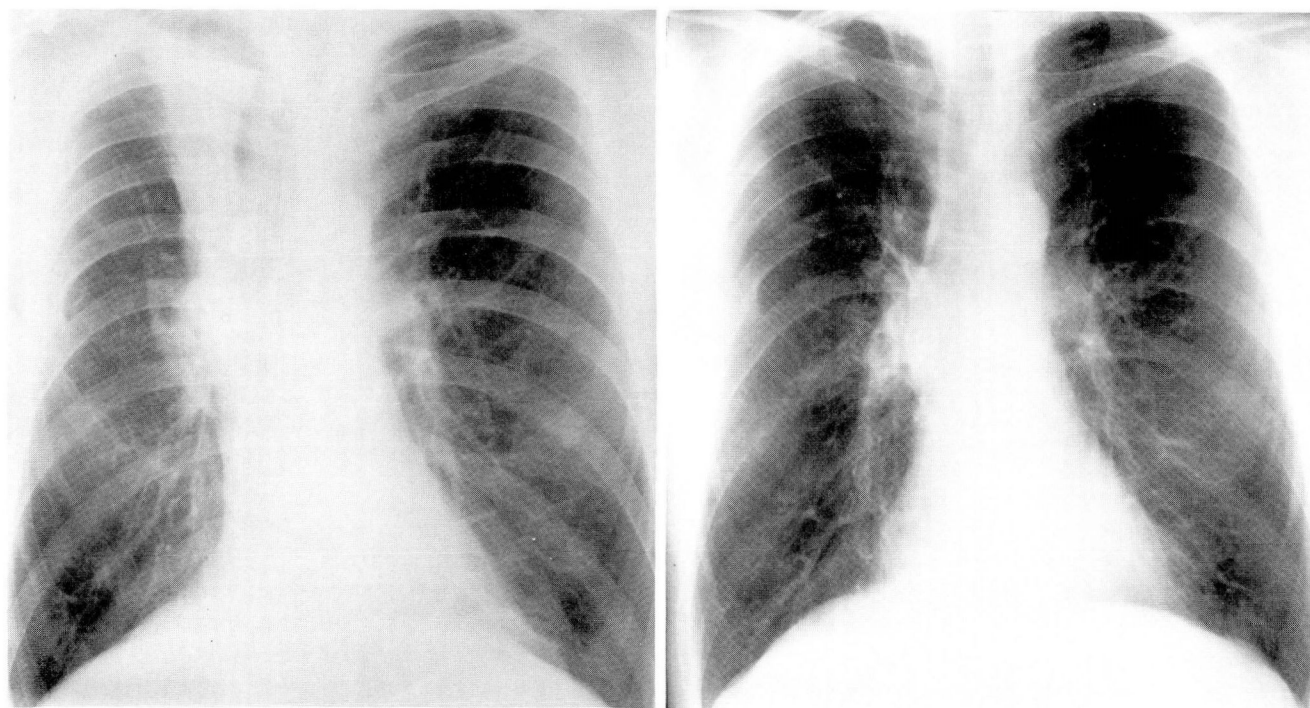
Differential diagnosis

Clinical entities that can be confused with allergic bronchopulmonary aspergillosis are noted (*Table 2*). These conditions usually can be distinguished on the basis of clinical, immunological, and other laboratory data.

Treatment

There is no proved effective therapy for allergic bronchopulmonary aspergillosis. Low-dose corticosteroid therapy, however, has been advocated by many investigators.^{38,40-42,47,49,53,57,78,79,81,107,125-127} Patients with allergic bronchopulmonary aspergillosis have been treated with emetine hydrochloride,²⁸ natamycin,¹²⁸ amphotericin B,¹²⁹ and nystatin,¹³⁰ with variable results. Some investigators who treated patients with corticosteroids observed that pulmonary eosinophilia recurred in patients who received less than 7.5 mg of prednisone per day.^{39,40,41,57} Edge et al²⁴ observed 5 patients with allergic bronchopulmonary aspergillosis who were able to discontinue corticosteroid therapy after beginning treatment with disodium cromoglycate (DSC). Safirstein et al⁵⁷ observed that treatment with DSC improved asthmatic symptoms, but did not prevent recurrent episodes of pulmonary infiltration. The lack of success of DSC therapy as attributed to its inability to reach areas of the lung that are damaged, and Safirstein suggested that airway obstruction and tenacious mucus might have impaired the intrapulmonary distribution of DSC and thus prevented its local inhibiting action. Rosenberg et al,¹²⁰ who followed patients for two months to nine years, reported that treatment with alternate-day prednisone therapy at a dose of 0.5 mg/kg resulted in clinical and radiological improvement and mild decrease in serum IgE levels, but did not prevent recurrence of the disease. The recurrent disease, however, responded to daily corticosteroid therapy. Daily corticosteroid therapy, consisting of prednisone (40-60 mg/day in divided doses, tapered to a maintenance dose of 20 mg every other day over several weeks and continued for several months) has been used. The serum IgE level was used as a prognostic indicator, and therapy was discontin-

ued when this reverted to normal or decreased significantly.^{79,131} Rosenberg et al¹³² described patients who were treated with corticosteroids demonstrated a gradual increase in IgE concentration after treatment had been discontinued. A sharp increase in IgE concentration developed at the time of new pulmonary infiltration. Increasing total serum IgE concentrations preceded the infiltration by several months. Similarly, specific IgG and specific IgE began to rise three months before the new infiltration appeared on radiographs. Specific IgE levels remained constant during the period of treatment, whereas specific IgG levels decreased in 1 patient and remained constant in another during the period of treatment. A recent study has suggested that patients with allergic bronchopulmonary aspergillosis whose serum IgE remains normal do not require chronic corticosteroid therapy.¹³³ Wang et al⁸⁰ observed 25 patients (average age, 2.6 years) with allergic bronchopulmonary aspergillosis for a period of one to 10 years after initial therapy with corticosteroids. Therapy consisted of prednisone (0.5 mg/kg of body weight for two weeks, then every other day for three months, with the dose subsequently tapered and discontinued after a period of three months). Eight patients had recurrent episodes of allergic bronchopulmonary aspergillosis; these exacerbations closely correlated with sharp increases in total serum IgE, which subsequently decreased after resumption of prednisone therapy. The increase in serum IgE preceded the pulmonary infiltrates in seven of 12 exacerbations. Acute asthma without pulmonary infiltrates was not associated with an increased serum IgE. Exacerbations developed during administration of beclomethasone dipropionate used for control of asthma. Twelve exacerbations occurred in 8 patients, with 2 patients having four and two recurrences, respectively. It was noted that (a) exacerbations are more likely to occur in certain patients, (b) serial management of the total serum IgE appears to be a useful indicator of disease activity in such patients, (c) patients with allergic bronchopulmonary aspergillosis, even in the presence of pulmonary infiltrates, may be asymptomatic, and (d) symptoms sometimes may develop without an increase in the serum IgE level or the development of pulmonary infiltrates. Follow-up evaluation consisted of obtaining a chest radiograph every four months for two years after the initial clearing of lung lesions, then every six months



A, B

Fig. 3. A. Muroid impaction in a patient with allergic bronchopulmonary aspergillosis, producing collapse of the apical segment of the right upper lobe.

B. Chest radiography obtained after the patient had been treated for allergic bronchopulmonary aspergillosis.

for two years, and then yearly if no exacerbations had occurred. IgE level was estimated every month for two years, then every two months if no exacerbation had occurred. Pulmonary function studies were done yearly. Some have reported successful treatment with beclomethasone dipropionate and triamcinolone estrionide.^{134,135} Turner-Warwick,⁴⁵ however, noted that therapy with beclomethasone was ineffective. In 13 patients with allergic pulmonary aspergillosis treated with diiodohydroxyquinoline (1.5 g/day for three weeks), Horsfield et al¹³⁶ observed marked clinical improvement in 4 patients, moderate improvement in 3, slight improvement in 3, and no improvement in 3. Finally, immunotherapy through interdermal hyposensitization has not been found effective;^{40,41} it has been suggested that it is contraindicated in this disease since such therapy, although useful in decreasing specific serum IgE, may produce an increase in circulating IgG antibodies, which could produce an adverse effect.⁴⁵

We recommend the use of prednisone (1 mg/kg of body weight for two to three months, tapered to 20 mg every other day over the next several weeks). The serum IgE level should be

used as a marker for the activity of the disease. Therapy can be discontinued when the IgE level has returned to normal or is substantially reduced. Following discontinuation of the treatment, serum IgE levels should be monitored at monthly intervals for the first few months or when the patient becomes symptomatic in order to detect early recurrence of the disease. In such an event, treatment should be repeated and continued for a longer period than the initial course.

MUCOID IMPACTION

Mucoid impaction of bronchi is defined as the obstruction of the proximal bronchi by plugs of inspissated mucus and exudates. Although the plugs are usually larger than those observed in allergic bronchopulmonary aspergillosis, there is considerable overlap between these two syndromes.⁹⁷ Mucoid impaction was first described by Shaw,¹³⁷ in 1951, and several reports have subsequently appeared.¹³⁸⁻¹⁴⁸ Mucoid impaction may be associated with allergic bronchopulmonary aspergillosis, asthma, other allergic states, bronchial adenoma, bronchial atresia, bronchogenic carcinoma, bronchogenic cyst, or may be idiopathic.¹⁴⁹ Clinically, 75% to 80% of patients

with mucoid impaction have asthma or chronic bronchitis.^{97,141,143,145} Mucoid impaction may develop in any age group; the age range was from 4 to 72 years in one series.⁹⁷ Males and females are equally affected. Presenting symptoms consist of fever, chest pain, hemoptysis, and upper respiratory tract infection. Of 85 patients reported by Urschel et al,¹⁴¹ 5 patients were asymptomatic; the abnormality was discovered by routine chest radiography. Similarly, six cases reported by Carlson et al¹⁴² were asymptomatic. Expectoration of sputum plugs has been reported in 44% of patients and is considered to be highly suggestive of the diagnosis.¹⁴³ Peripheral eosinophilia frequently is present. *Aspergillus* hypersensitivity has not been investigated in many of the reported patients, and it is difficult to ascertain how many of the cases were associated with aspergillosis.¹⁴¹ In 1960, Johnson and Sita-Lumsden¹⁵⁰ reported four cases of mucoid impaction and observed positive immediate skin reactions to *Aspergillus* extracts in 2 and a sputum culture yielding *Aspergillus* in 1 of the patients. None of the patients had positive precipitins. Other investigators have reported a positive type 1 skin reaction, *Aspergillus* precipitins, and sputum cultures positive for *Aspergillus* in patients with mucoid impaction.^{71,151}

Radiological abnormalities may be directly related to mucus plugs or to the effects of obstruction or both.^{142,144,146,147} (Figs. 3, A and B). There is an upper lobe preponderance. In 85 patients investigated by Urschel et al,¹⁴¹ upper lobe involvement was present twice as often as lower lobe involvement. The chest radiograph shows round or oval densities that are difficult to differentiate from a neoplasm; however, the image may also reveal features similar to those observed in allergic bronchopulmonary aspergillosis.

Pathological findings

Pathological examination of resected specimens revealed characteristic lesions, both in involved bronchi and in distal parenchyma. Changes consistent with that of asthmatic bronchitis are observed in most cases.^{140,152} The impacted segmental or subsegmental bronchi are dilated and have thin and fibrotic walls containing atrophied cartilage and mucus glands.^{138,143} A peribronchial eosinophilic infiltrate is common. The mucus plugs or casts may be as large as 2.5–6.0 cm. They are gray to greenish-yellow

in color.^{141,143,148,152} Microscopically, the plugs consist of mucus, fibrin, eosinophils, neutrophils, and epithelial cells in various stages of necrosis. Frequently, the parenchyma distal to the obstructed bronchi may demonstrate organizing pneumonia.¹⁵² Patients with cystic fibrosis have an increased incidence of mucoid impaction.¹⁵³ Many postulates have been advanced to explain the pathogenesis of mucoid impaction. Most consider that it develops from allergic bronchitis, resulting in hypersecretion of viscid mucus.^{138,141,146,152} Other factors thought to contribute include excessive dehydration of secretions,¹⁴¹ excessive resorption of water by the bronchial mucosa,¹⁴³ and increased DNA content of the mucus.¹⁰³ The frequent association between mucoid impaction and allergic bronchopulmonary aspergillosis^{52,150,151,154} suggests that *Aspergillus* hypersensitivity may play some role in its pathogenesis. *Aspergillus* can be cultured from the sputum in some patients. Campbell and Clayton,³⁸ however, note that the sputum cultures may be negative despite the presence of fungus in the lungs, since there is expectoration of a small number of fungi because of the tendency of macrophages to engulf hyphae.

Treatment

Proper hydration must be carried out and bronchopulmonary hygiene must be maintained for all patients. Corticosteroids have been shown to be effective only in cases where mucoid impaction is the result of allergic bronchopulmonary aspergillosis.¹³⁸ Administration of mycolytic agents may aid in clearing mucus plugs.

EXTRINSIC ALLERGIC ALVEOLITIS

This group of hypersensitivity lung reactions, of which farmer's lung is a prototype, also is described as microgranulomatous hypersensitivity reaction and extrinsic allergic pneumonia.⁹⁷ This syndrome develops predominantly in non-atopic subjects.⁵⁸ Riddle and Grant¹⁵⁵ described the syndrome in a 42-year-old malt worker whose sputum yielded *Aspergillus clavatus* and who had serum precipitating and complement fixing antibodies directed against an extract of *A. clavatus*. The patient also experienced an Arthus reaction (type III) following intradermal injection of *A. clavatus* extract. Clinical symptoms recurred when he was challenged by inhalation of *A. clavatus* spores. According to Riddle et al,¹⁵⁶ Filip

and Barborik described a similar syndrome in 1 man and 17 women which developed after the 18 were heavily exposed to *A fumigatus* spores. A causal relationship between extrinsic allergic alveolitis and *Aspergillus versicolor* has been reported by Rhudy et al.¹⁵⁷ Johnson et al.¹⁵⁸ described a 70-year-old farmer who had multiple episodes of late-onset (four to six hours) asthma following exposure to *A niger* spores. Many other reports describing the association between extrinsic allergic alveolitis and a heavy exposure to certain species of *Aspergillus* have appeared.^{125,126,157-166} Katz and Kniker¹⁶⁷ reported a 14-month-old boy who had features of both allergic bronchopulmonary aspergillosis and extrinsic allergic alveolitis; they suggested that this disorder may be part of a spectrum of hypersensitivity reactions in the lungs.

Clinical features

The patient may present either with acute or chronic symptoms, depending upon the nature of the exposure. If the exposure has been heavy, the onset is sudden^{58,125,155,158} and the clinical features resemble an influenzalike illness, consisting of fever, malaise, cough (which usually is nonproductive), myalgias, chills, dyspnea, and chest tightness. There may be mild hemoptysis. The patients have both constitutional and reversible airway symptoms. In chronic exposure, exertional dyspnea is the principal system. The patient also may have striking weight loss, but the constitutional symptoms generally are less prominent.

Radiological features include fine nodular mottling, which may be diffuse or may be limited to one or two zones. Large patchy opacities may be present; these are due to the confluence of the nodular lesions. There may be evidence of pulmonary fibrosis if the exposure has been chronic. Pulmonary function studies demonstrate a restrictive pattern with decreased diffusing capacity.

Pathology

The histopathology of the acute stage consists predominantly of interstitial infiltrates of lymphocytes and histiocytes that concentrate about and also involve the bronchial wall.⁹⁷ An antecedent stage is characterized by alveolar damage with hyaline membrane formation. Exudation of fibrin and a predominant small mononuclear cell

infiltration may be present. Minute noncaseating granulomas appear as the disease progresses.^{97,168} Although infiltration of the vessels has been observed, necrotizing vasculitis does not occur. Yocum et al.⁵⁸ described a 37-year-old farmer's wife in whom extrinsic allergic alveolitis developed three weeks after heavy exposure to *A fumigatus* while she was bagging infected oats. Histopathological studies performed on a lung specimen obtained by transbronchial biopsy revealed consolidation of the parenchyma with an infiltration of plasma cells, lymphocytes, and a moderate number of eosinophils. Numerous granulomas with central necrosis were observed throughout the lobule; the central necrotic areas contained leukocytes, eosinophils, and necrotic debris. The granulomas appeared to be confined to respiratory bronchioles, and alveolar ducts were surrounded by epithelial cells and occasional giant cells. Branching septate hyphae characteristic of *A fumigatus* were present within the necrotic centers of the granulomas. There was mild edema and infiltration of vessels, with lymphocytes and plasma cells in the intermedia and adventitia. Patterson et al.¹²⁵ reported the histopathological study of a 54-year-old patient who died of hypersensitivity pneumonitis after exposure to *A flavus* in moldy corn. The most striking histological feature was the presence of numerous organizing endobronchial nodules involving medium- and small-sized bronchi. These frequently extended proximally and distally within the bronchial lumen, and some branched within the bronchus. Collections of eosinophils occasionally were present within the nodules. Granulomas, giant cells, crystals, or foreign bodies were absent, and significant interstitial inflammation was not present. Small atelectatic areas were present throughout. These investigators failed to demonstrate *Aspergillus* spores, mycelia, or other evidence indicating its presence. The chronic stage, which follows repeated exposures, reveals interstitial fibrosis and cystic changes.

Immunology

Serum precipitins to *Aspergillus* extracts are invariably present.^{58,125,155,158,160,165,166,169} The presence of a type I reaction (immediate reaction), dual response, and type I and type IV reactions have been reported.^{58,156,158,168} Inhalation challenge studies have been demonstrated to reproduce the illness.^{165,170} Increased lymphocyte blast transformation has been observed.

Yocum et al⁵⁸ suggested that a type IV immunological reaction may be responsible for the pathogenesis of this syndrome. The immunopathogenesis of the syndrome, however, remains controversial.

Treatment

In patients with the acute illness, corticosteroid therapy usually results in rapid resolution. The patient may demonstrate spontaneous resolution of acute lung changes once removed from exposure to the causal agent. Recurrent alveolitis and chronic disease may be prevented by avoidance of further exposure.

BRONCHOCENTRIC GRANULOMATOSIS

This condition is characterized by granulomatous and destructive lesions of bronchi and bronchioles. In contrast to other forms of granulomatosis, the vessels in bronchocentric granulomatosis are involved only incidentally. There is no extrapulmonary involvement. In 1973, Liebow⁹⁴ described 9 patients, whose ages ranged from 10 to 74 years (most between 28 and 48 years old), with bronchocentric granulomatosis. There were nearly equal numbers of males and females. Three of the patients were asymptomatic, 2 had had asthma since childhood, and 1 (20 years old) had had recurrent migratory pulmonary infiltrates since age 17. The remaining 3 persons had various symptoms and signs, consisting of cough, migratory chest pain, and recurrent bouts of pneumonia. Laboratory investigations of these patients were unremarkable. Katzenstein et al⁹⁷ described clinical and pathological features in 23 patients with bronchocentric granulomatosis. Ten of the patients had a strong history of asthma, dating to childhood. Three had mucoid impaction, and 9 had fungal hyphae present in bronchial lesions or within bronchi. The male to female ratio was 7:3. The average age was 22 years (range, 9 to 48 years old). The presenting symptoms were productive cough, chest pain, fever, anorexia, and general malaise. Only 1 patient had hemoptysis. Laboratory studies demonstrated a mild to moderately elevated erythrocyte sedimentation rate (24–73 mm/hr in 3 patients), negative antinuclear antibodies, and negative rheumatoid factor (5 patients). Nine patients had peripheral eosinophilia, ranging from 6% to 46%. The dual skin test for *Aspergillus* was positive in 1 patient, and serum precipitins to *Aspergillus* were positive in 3 patients. One

of 7 patients had precipitins positive for *Candida*. Sputum cultures yielded *A niger* in 1 and *Candida albicans* in 1. A nonasthmatic group of patients consisted of 6 men and 7 women. The average age of onset of symptoms was 50 years (range, 37 to 76 years old). These patients had no evidence of atopy. One patient had chronic urticaria, and 1 had a history of interstitial pneumonia and bilateral lacrimal gland enlargement, which had resolved with corticosteroid therapy. One patient had a diagnosis of sarcoidosis established by liver biopsy. Six of the nonasthmatic patients had minimal symptoms (nasal congestion, nasal discharge, fatigue, and cold symptoms). One patient complained of cough, hemoptysis, and malaise. Three patients had acute symptoms, consisting of fever, malaise, cough, and dizziness. Wheezing developed in 2 patients during the illness. Peripheral eosinophilia was present in 2 patients. The erythrocyte sedimentation rate was moderately elevated (40–70 mm/hr) in 4 patients. The rheumatoid factor was negative in 3 patients tested, and the ANA was negative in 2 patients tested. *C albicans* was isolated from the sputum in 2 patients. Precipitins were negative in the patients tested. Hanson et al¹⁷¹ reported a case of bronchocentric granulomatosis associated with allergic aspergillosis in a 14-year-old patient with a history of allergic rhinitis and asthma. He presented with fatigue, purulent sputum production, wheezing, occasional fever, weight loss, anorexia, and progressive dyspnea. The erythrocyte sedimentation rate was 81 mm/hr. There was peripheral eosinophilia (1,388 eosinophils/mm³), a serum IgE level of 4,675 ng/mL, precipitin bands to *Aspergillus* antigen, a sputum culture yielding *Aspergillus*, a positive dual skin test, and positive specific IgE antibodies. The radiological features in both the asthmatic and nonasthmatic patients reported by Katzenstein et al⁹⁷ were similar. These consisted of consolidation or atelectasis of an entire lobe in 5 patients, consolidation or atelectasis or less confluent pneumonic infiltrates involving less than one lobe in 16 patients, single or multiple nodular masses in 5 patients, and small nodules or a mixed nodular and linear pattern in 5 patients. Segmental bronchial obstruction was observed in 2 patients, and bronchiectasis was demonstrated on bronchograms of 1 patient.

Pathology

Macroscopic findings. The lumina of the small bronchi and bronchioles are filled with yellow-

white "cheesy" material.⁹⁷ The affected bronchi appear as rounded and elongated branching structures. The presence of unaffected pulmonary arteries adjacent to the necrotic lesion confirms the location of the lesion in the airways. Katzenstein et al⁹⁷ found mucoid impaction in 4 patients; destructive cheesy yellow lesions in these patients were present distal to the mucoid impaction. Hanson et al¹⁷¹ observed multiple areas of consolidation and large amounts of mucopurulent material in major bronchi; they did not observe mucus plugs.

Microscopic findings. Liebow⁹⁴ described focal ulcerations of some large bronchi. The ulcers were shallow and lined by granulation tissue and often by palisades of epithelial cells. Katzenstein et al⁹⁷ described the presence of cellular debris, often mixed with eosinophils, neutrophils, desquamated lining cells of the distal airways, and red blood cells within the lumina of the conducting airways internal to the palisades of epithelial cells. Large, deeply eosinophilic clumps of conglomerated cellular debris were found in some granulomas and in the lumina of the bronchioles. Remarkable foreign body giant cell reactions to the clumps of eosinophils were present in four cases. A dense infiltrate, consisting of lymphocytes, plasma cells, and eosinophils within the granulation tissue, usually surrounded by palisades of epithelial cells, was in most instances, confined to peribronchial tissue, but occasionally extended to the distal parenchyma. In many instances, alveoli were filled with foamy macrophages behind obstructed bronchioles. Fungal hyphae were demonstrated by a Gorcott silver stain within the resected lung tissue in 9 patients. However, this was not considered to be consistent with frank tissue invasion. All of the patients were asthmatics. The remaining 14 of the 23 patients did not demonstrate evidence of the presence of fungus. Acid-fast bacilli were absent in all patients. Similar microscopic changes were observed in 1 patient by Hanson et al.¹⁷¹ Pulmonary arteries adjacent to the granulomatous lesion occasionally were involved, but more frequently they were infiltrated with lymphocytes and plasma cells, with intimal thickening, predominantly on the side adjacent to the involved bronchus, suggesting that the vasculitis was the result of the bronchocentric lesion.

Treatment

Eight of 13 nonasthmatic patients reported by Katzenstein et al⁹⁷ underwent surgical resection.

Five of these patients, who were subsequently observed for one to 12 months, remained clinically well except for recurrent pulmonary infiltrates. One patient who had received corticosteroids postoperatively did not experience a recurrence. One patient in whom hematuria developed was initially treated with antituberculosis drugs and subsequently with cyclophosphamide and prednisone, but died after 15 months. The autopsy revealed focal glomerulonephritis, but no evidence of active pulmonary involvement. One patient received azathioprine for 22 months and became asymptomatic with resolution of the infiltrates as shown on the radiograph. Two patients received no specific therapy and had no recurrences during follow-up periods of 14 and 21 months, respectively. Eight of 10 asthmatic patients underwent lobectomy. Five of these patients received bronchodilators and antibiotics postoperatively and remained free of recurrence for four months to four years. Three patients who were treated with corticosteroids postoperatively demonstrated both symptomatic and radiographic improvement. One of the 3 patients, observed for 11 years, had multiple recurrences, each time responding to the administration of corticosteroids. Two of the 10 asthmatic patients who did not undergo surgical treatment received corticosteroids, in addition to standard treatment for asthma; both the patients showed clinical and radiographic improvement. A cavitary lesion developed in the left upper lobe of 1 patient who underwent surgical resection; the lesion was treated successfully with corticosteroids. Hanson et al¹⁷¹ used surgical resection, followed by administration of corticosteroids, with successful results.

In summary, the treatment for a solitary lesion is surgical resection, followed by corticosteroid treatment in case of recurrence. Patients presenting with multiple lung lesions should receive steroids after the diagnosis has been established.

EOSINOPHILIC PNEUMONIA

In 1952, Crofton et al¹⁷² introduced the term "pulmonary eosinophilia" to describe patients in whom transient pulmonary infiltrates occurred in association with peripheral blood eosinophilia. This condition has also been called pulmonary infiltrates with eosinophilia (PIE). Katzenstein et al⁹⁷ differed with the definition given by Crofton et al¹⁷² and pointed out that, although most patients may have peripheral eosinophilia ranging

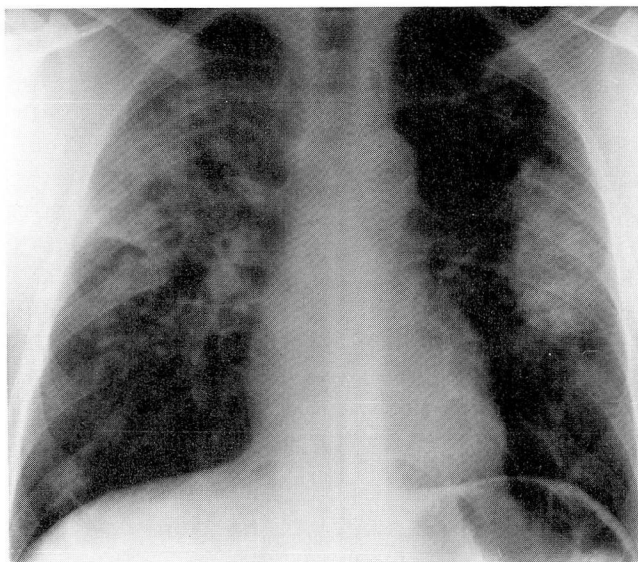


Fig. 4. Eosinophilic pneumonia. Note that infiltrates mainly involve the peripheral lung field, while the central zone is relatively spared (inverse pulmonary edema pattern).

from 25% to 75%, there are instances where the eosinophil count may not be elevated. Crofton et al¹⁷² attempted to categorize the various entities composing this syndrome as follows:

1. Symptomatic pulmonary eosinophilia (Loeffler's syndrome),
2. Chronic eosinophilic pneumonia,
3. Tropical eosinophilia,
4. Pulmonary eosinophilia with asthma, and
5. Vasculitis.

This classification is primarily based on clinical findings rather than on etiological factors. This disease is perhaps most commonly associated with hypersensitivity to *A fumigatus*. Scadding¹⁰⁸ further clarified the picture by distinguishing the clinical features of eosinophilic infiltration occurring in extrinsic and intrinsic asthmatic patients. In one series reported by McCarthy and Pepys,^{40,41} allergic bronchopulmonary aspergillosis was responsible for 80% of 143 patients with this syndrome; in the remainder, the cause was not known. In another series of 65 patients with asthma and eosinophilic pneumonia, Middleton et al¹⁷³ evaluated 32 patients who had aspergillosis. These authors observed that the patients with allergic aspergillosis associated with longstanding asthma and the least favorable prognosis. Patterson et al⁹⁰ observed elevated serum IgE concentrations when this syndrome was associated with allergy to *Aspergillus*. In contrast,

the serum IgE in nonasthmatic patients with eosinophilic pneumonia (except patients with helminthic infestation) was not elevated. Turner-Warwick et al¹⁷⁴ described pulmonary eosinophilic pneumonia in asthmatic patients who had negative immediate skin reactions. It was also observed in nonasthmatics who had no predisposing factors such as drug ingestion or parasitic or fungal infections. These patients have been stated to have cryptogenic eosinophilic pneumonia if periarteritis nodosa does not develop. Clinical features in both asthmatics and nonasthmatics usually are those of a slight productive cough, weight loss, and anorexia. Fever usually is absent, but mild and, rarely, high fever may occur. Patients with asthma frequently have systemic disease, including hepatosplenomegaly and hilar node involvement.¹⁷⁴ Laboratory abnormalities consist of an elevated sedimentation rate, anemia, mild to moderate leukocytosis usually not exceeding 20,000/mm³, and eosinophilia, which may exceed 75% but is not often greater than 25%. Eosinophilia may be absent. The degree of eosinophilia in the blood and sputum tends to be greater in patients with cryptogenic pulmonary eosinophilia than in allergic bronchopulmonary aspergillosis.¹⁷⁵ The pulmonary radiograph shows infiltrates that are of the pneumonic type and have a striking tendency to involve different portions of the lung from time to time.

The term "chronic eosinophilic pneumonia" was coined by Liebow and Carrington¹⁷⁶ to describe features of a group of patients with prolonged eosinophilic pneumonia with or without asthma. Pulmonary infiltrates in such patients tend to be relatively stable and clear with treatment, but recur subsequently in the same region.¹⁷ A characteristic radiographic appearance, described by Carrington et al¹⁷⁷ as a photographic negative of pulmonary edema, consists of peripheral density adjacent to the pleura with a clear central zone (Fig. 4).

The histology of eosinophilic pneumonia, despite a heterogeneous etiology, is characterized by the filling of alveoli with eosinophils and large mononuclear cells and by interstitial infiltration of eosinophils and lymphocytes and plasma cells. Eosinophilic abscesses, often with necrotic centers surrounded by a granulomatous capsule, may be present and occasionally may involve the small bronchioles.⁹⁷ The small bronchioles may also demonstrate bronchiolitis obliterans with eosin-

ophilic infiltration and even granulomatous reaction.¹⁷⁶ Warnock et al⁶⁵ described pathological findings in a patient with chronic eosinophilia with allergic aspergillosis. These findings consisted of large granulomas with central necrotic cellular debris and mature eosinophils surrounded by multinucleated giant cells and epithelioid cells. Proximal cylindrical bronchiectasis, characteristic of allergic bronchopulmonary aspergillosis without evidence of necrotizing angitis, was present. Cellular infiltrates of vessels, particularly of venules, frequently are present, but the vasculitis usually is not of the necrotizing type.^{176,177} Immunological findings in patients with eosinophilic pneumonia and allergic aspergillosis are similar to those of patients with allergic bronchopulmonary aspergillosis. Patients with cryptogenic pulmonary eosinophilia, however, do not demonstrate any abnormality. McCarthy and Pepys¹⁷⁵ did not discover any immunological abnormality in 27 patients with cryptogenic pulmonary eosinophilia. Assem and Turner-Warwick⁴⁸ found no evidence of specific antibody to *A fumigatus* in 6 patients with cryptogenic pulmonary eosinophilia. High levels of IgE have been observed in patients with acute eosinophilic pneumonia. McEvoy et al¹⁷⁸ noted that high levels of IgE are present only during acute episodes and that the levels return to normal during natural or corticosteroid-induced remission.

Treatment

Treatment consists of corticosteroid therapy and the response to this usually is dramatic. The disease may recur after the discontinuation of treatment. Golbert and Patterson⁴⁹ do not believe that corticosteroids prevent further episodes. Safirstein et al⁵⁷ reported a 65% recurrence rate in patients who did not receive corticosteroids as compared to 20% who received continuous corticosteroid therapy. Effective treatment, however, involves the removal of the causative antigen, if identified, or removal of the patient from the contaminated environment.

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