Pulmonary Aspergillosis: Immunological Syndromes*

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Aspergillus is found everywhere in nature. This fungus is present in gardens and garages, attics and basements, furniture and bedding as well as house dust. It is also the most common laboratory contaminant. Of the 358 species that belong to the genus *Aspergillus*, only *A. fumigatus* and *A. niger* produce disease in humans. Under certain conditions, however, *A. clavatus, A. flavus, A. versicolor, A. oryzae* and a few other species can cause infection in insects, birds and domestic animals.

Although *Aspergillus* can affect any organ system, the respiratory tract is involved in more than 90 per cent of afflicted patients. Pulmonary aspergillosis, depending on whether the host is or is not atopic or immunosuppressed, may be classified under four broad categories encompassing at least a dozen different clinical syndromes (Table 1). Some of these clinical syndromes are well defined and common; others are unusual and controversial. The key points in the pathogenesis, immunology, diagnosis and treatment of each syndrome are summarized in Tables 2 and 3.

Table 1 Pulmonary aspergillosis: immunological syndromes

1. **Allergic or Hypersensitivity Reactions**
   - Allergic asthma
   - Allergic bronchopulmonary aspergillosis (ABPA)
   - Extrinsic allergic alveolitis (Malt-worker's lung)
   - Bronchocentric granulomatosis
2. **Saprophytic Colonization**
   - Mycetoma or fungus ball
3. **Invasive (Infective) Aspergillosis**
   - *Aspergillus* pneumonia
   - Lung abscess and multiple cavities
   - *Aspergillus* bronchitis
   - Infarction
   - Pleural effusion and empyema
   - Chronic necrotizing pulmonary aspergillosis (CNPA)
4. **Chemical or Toxic Pneumonitis**
   - Mycotoxicosis

ALLERGIC OR HYPERSENSITIVITY REACTIONS

Allergic asthma

The fungal material – spores and hyphae – can provoke typical asthma attacks in an atopic individual. In the United States, such episodes are more common between October and February, when the atmospheric *Aspergillus* spore count is high, than at other times of the year.

An intracutaneous test using *Aspergillus* antigen will produce an immediate wheal-flare reaction in asthmatic patients allergic to *Aspergillus*. Moreover, inhalation of the offending antigen will produce rapid airway obstruction. In making the diagnosis, however, physicians should be cautious since from 30 to 40 per cent of the patients with uncomplicated asthma may also have a positive reaction to the *Aspergillus* skin test. Precipitating antibodies are usually absent in such patients, but present in those with allergic bronchopulmonary aspergillosis (ABPA) and aspergillomas.

The conventional bronchodilator drugs are effective in treating this type of allergic asthma. Disodium cromoglycate may also be beneficial

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Table 2 Pulmonary aspergillosis: immunological syndromes

Syndromes	Immunologic mechanism	Host		Treatment
		Atopic	Immuno-suppressed	
Allergic asthma	Hypersensitivity (type I)	Yes	No	Cromolyn sodium, bronchodilators
Allergic bronchopulmonary aspergillosis (ABPA)	Hypersensitivity (types I and III)	Yes	No	Corticosteroids, cromolyn sodium, bronchodilators
Extrinsic allergic alveolitis (malt-worker's lung)	Hypersensitivity (types III and IV)	No	No	Corticosteroids, avoidance of exposure
Bronchocentric granulomatosis	Hypersensitivity (?)	in some cases	No	Corticosteroids
Aspergilloma	Saprophytic colonization	No	No	Surgery only if haemoptysis is present, 5 FC
Pneumonia, lung abscess, bronchitis, infarction	Invasive (infective) localized disease	No	Yes	Amphotericin B
Multiple cavities, pleural effusion	Invasive (infective) disseminated disease	No	Yes	Amphotericin B
Chronic necrotizing pulmonary aspergillosis	Invasive chronic	No	Yes	Amphotericin B, 5 FC
Mycotoxicosis	Chemical or toxic pneumonitis	No	No	Corticosteroids

for some patients. Corticosteroids may be used for patients who do not respond to the usual therapy. Desensitization is not generally recommended.

Allergic bronchopulmonary aspergillosis (ABPA)

The ABPA syndrome occurs almost exclusively in atopic asthmatic individuals. Affecting the bronchial walls and the peripheral parts of the lung, it causes an acute migratory infiltration of the lung and then a variety of irreversible changes that cause chronic dysfunction. Cor pulmonale may occur in about 1 per cent of the patients.

In Britain, ABPA has been reported in 22 per cent of hospitalized asthmatic patients.[1] The disease is not diagnosed as frequently in the United States, which may be due to a failure to recognize it and perform appropriate diagnostic tests. Physicians should suspect this syndrome in every patient with asthma and a pulmonary infiltrate. ABPA usually manifests itself with a low-grade fever, wheezing, cough with the production of golden brown sputum plugs and progressive shortness of breath. Physical examination reveals signs of airway obstruction and patchy crepitant rales. Lung function tests usually reveal an obstructive defect.

Eosinophilia in blood and sputum is common. Direct examination of the sputum plugs often will disclose hyphae and fungal spores. A sputum culture positive for *Aspergillus*, however, does not always mean that the patient is suffering from allergic aspergillosis, since *Aspergillus* is so commonly found in expectorated material. Lung biopsy specimens usually show infiltration by mononuclear cells and eosinophils.

Chest radiographs reveal transient pulmonary infiltrates that shift from one place to another (Fig. 1). Segmental, lobar, or total collapse of the lung due to mucous plugging may occur. "Tram-line" shadows, "gloved-ring" shadows, or "ring" shadows due to inflammation and thickening of the bronchial wall are also often present (Fig. 2). In the late stages of ABPA, loss of volume of the upper lobes, "honeycombing" and extensive bronchiectasis may be seen; bronchograms may reveal a characteristic saccular dilatation of proximal or medium-sized bronchi (Fig. 3).

The pathogenesis of the disease is believed to involve the inhalation, trapping and subsequent germination of *Aspergillus* spores in viscid secretions in the airways of an ato-

Table 3 Immunologic and diagnostic tests in *Aspergillus*-related syndromes

Syndromes	Type I reaction		Type III reaction		Type IV reaction	Other diagnostic tests
	Immediate cutaneous hypersensitivity	Serum IgE	Delayed (Arthus) skin reaction	Precipitating antibodies		
Allergic asthma	Positive	Increased	Absent	Absent	Absent	Reversible airway obstruction
Allergic bronchopulmonary aspergillosis (ABPA)	Positive	Markedly increased	Present	Present	Absent	Bronchogram, inhalation challenge
Extrinsic allergic alveolitis (malt-worker's lung)	Usually positive	Usually normal	Present	Present	Present	Lung histology, inhalation challenge
Bronchocentric granulomatosis	May be positive	May be increased	May be present	May be present	Absent	Lung histology
Aspergilloma	May be positive	Normal	Present	Very high		Chest x-ray
Pneumonia, lung abscess, bronchitis, infarction	May be positive	Normal	Absent*	Absent*		Sputum, blood, urine cultures
Multiple cavities, pleural effusion	Usually negative*	Normal	Absent*	Absent*		Sputum, blood, urine cultures
Chronic necrotizing pulmonary aspergillosis	–	–	–	May be present		Lung biopsy
Mycotoxicosis	Negative	Normal	Absent	Absent		Lung biopsy

***The literature is divided, but many of these tests are positive if the highest-quality antigen is used and a research laboratory performs the tests.**

pic individual. Following germination, the organisms vegetate in the bronchial lumen and produce high concentrations of antigens. The host response, with production of IgE and IgG, sets in motion a series of antigen-antibody reactions that result in eosinophilic infiltration and bronchial wall damage. It is immune-complex injury that produces bronchiectasis, and the presence of IgE immunoglobulin is essential to enhance the tissue-damaging effect of immune complexes.

Diagnosis of ABPA involves immunologic confirmation in a fitting clinical and radiographic setting. The presence of an immediate (type 1) wheal-flare reaction is a necessary finding in the diagnosis of ABPA. If the immediate result of skin reactivity testing is negative, it is unlikely that the patient has ABPA. An Arthus (type 3), or late, skin reaction occurs in most of the patients.[2]

Serum precipitating antibody, which is of the IgG type, is present in most patients with ABPA. However, the presence of precipitating antibody is not diagnostic because a high concentration of the antibody can be found in patients with fungus balls and with allergic alveolitis, as well as in patients with cystic fibrosis. Serum IgE level is significantly elevated in patients with ABPA; this phenomenon is helpful in diagnosing and monitoring the activity of the disease because there is a direct correlation between disease activity and serum IgE level.[3]

The most effective treatment of ABPA is with corticosteroids. Continuous oral corticosteroid treatment diminishes the frequency of the acute episodes and reduces the likelihood of permanent and severe damage; for this reason, prednisone, 40 mg daily, is prescribed for a period of four to eight weeks. Disodium cromoglycate is another therapeutic option. It is also important to use bronchodilators, hydration and physiotherapy to remove the viscid secretions and thick plugs of sputum. Early diagnosis of ABPA is essential so that mandatory treatment with corticosteroids can be instituted before advanced

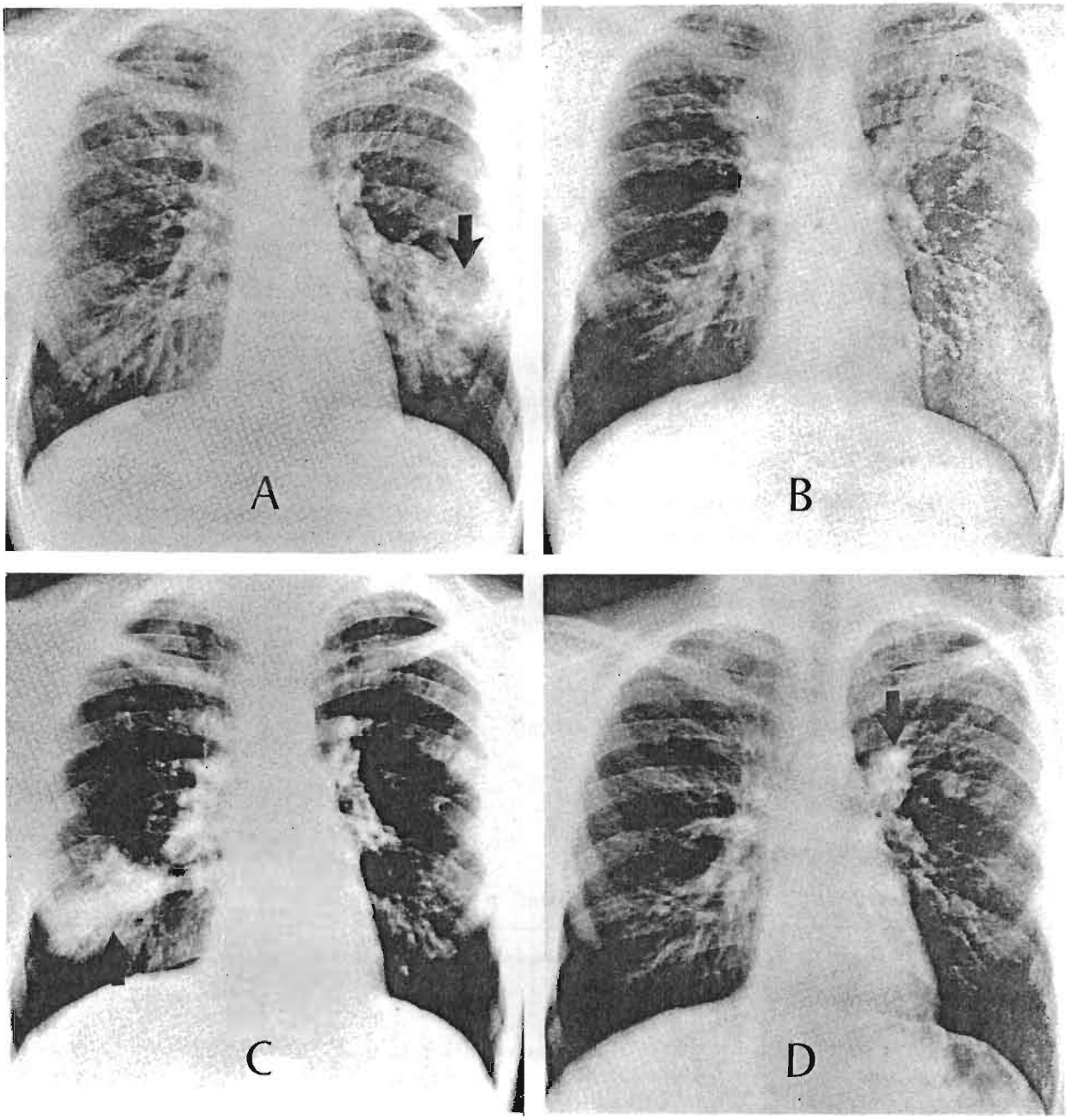

Fig. 1 A, B, C, D These four chest radiographs show the characteristic transient or fleeting pulmonary infiltrates in a young man with bronchial asthma and allergic bronchopulmonary aspergillosis.

irreversible lung damage occurs.

Extrinsic allergic alveolitis

This disease, also known as malt-worker's lung, occurs mainly in nonatopic individuals. It is found among workers in the whisky and beer brewing industries, where germinating barley may be contaminated with *A. fumigatus* and *A. clavatus*. Inhalation of fungal proteins produces a clinical picture similar to that of farmer's lung.[4]

After the initial exposure, there is a latent period of highly variable duration – from weeks to years – during which appropriate precipitating antibodies are formed. Subsequent exposure to *Aspergillus* particles then produces systemic and pulmonary reactions. The patient himself may recognize the cause-and-effect relationship because of the characteristic four to six hours that elapse between the time of exposure and the appearance of symptoms.

There are four modes of presentation. Acute episodes of fever, cough, tightness of chest and dyspnoea may occur in about 30 per cent of patients. Progressive dyspnoea may be seen in 50 per cent of patients. Atopic individuals present an asthma-like picture. A mixed presentation characterizes 10 per

cent of patients.

On examination, the acutely ill patient may be cyanotic and have tachycardia. Crepitations at the lung bases are present, but wheezing is usually absent. In advanced cases of the disease, there may be evidence of right heart failure.

The chest radiographs typically shows diffuse, fine, nodular infiltration or large patchy densities in the acute stage of the disease, and interstitial fibrosis with a reticulolinear pattern and honeycombing in chronic cases (Fig. 4). Often, the chest radiograph is normal. In the acute phase, a lung biopsy specimen will reveal a granulomatous reaction associated with infiltration by lymphocytes and mononuclear cells. Fibrosis and cyst formation occur in chronic cases. Precipitating antibodies (IgG) against *Aspergillus* are present in about 90 per cent of the patients with extrinsic allergic alveolitis.

Lung function studies reveal a restrictive ventilatory defect due to reduced pulmonary compliance. The vital capacity is low and there is a proportionate reduction in the forced expiratory volume. Diffusing capacity may be markedly reduced. Hypoxia and hyperventilation, with a consequent lowering of the arterial carbon dioxide tension, are frequent.

Corticosteroids are effective for controlling symptoms in the acute stage of the disease. Further exposure to the *Aspergillus* antigen should be avoided in order to prevent pulmonary fibrosis.

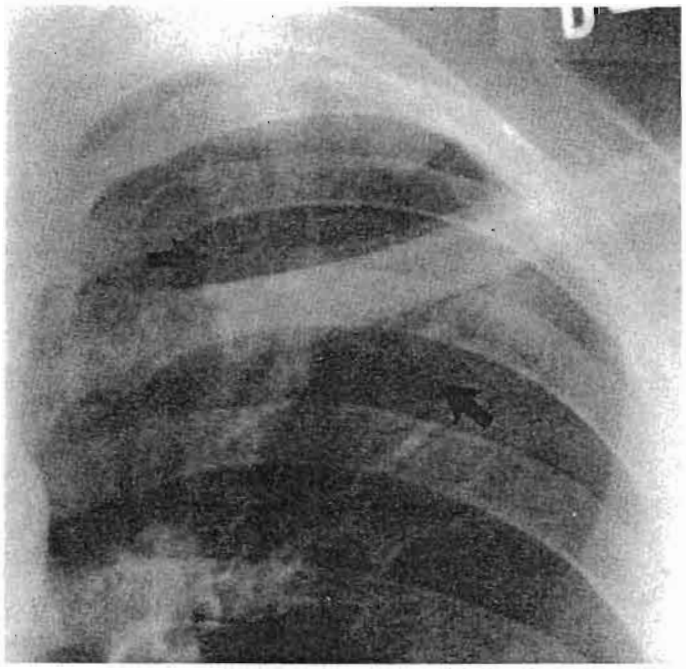

Fig. 2 'Glove-finger' and 'ring' shadows due to inflammation, dilatation and thickening of the bronchi.

Bronchocentric granulomatosis

This pathologic entity is characterized by the presence of bronchocentric granulomatous lesions in the bronchial mucosa, particularly of the conducting airways. The lesions consist of heavy eosinophilic infil-

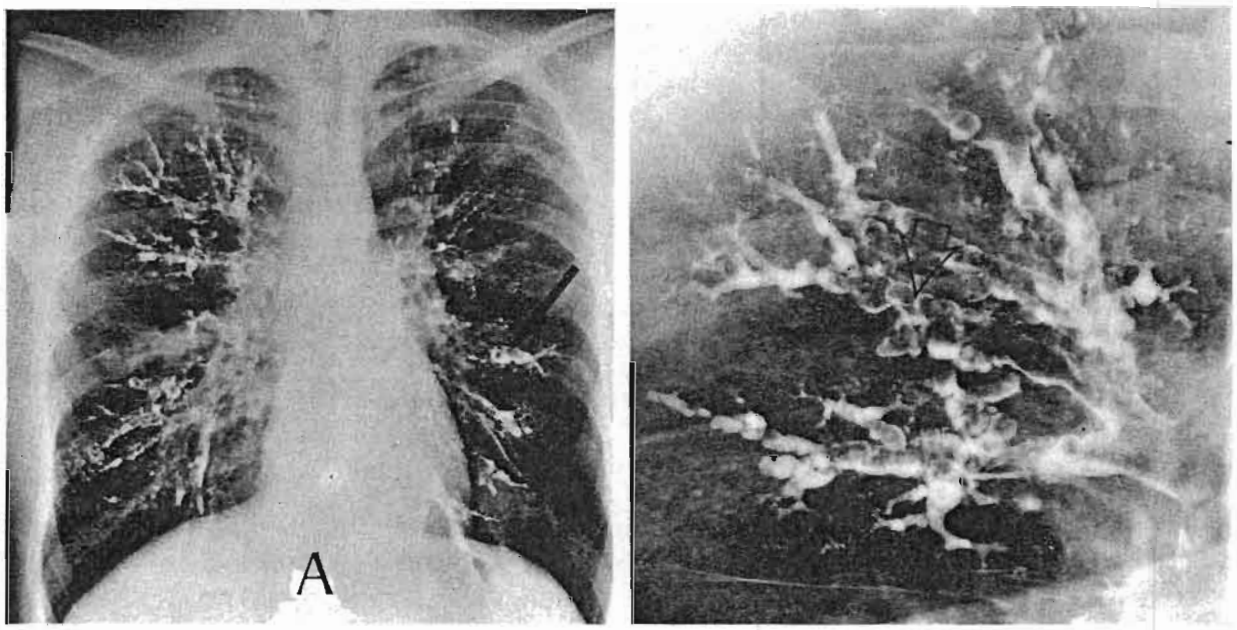

Fig. 3 A, B Extensive bronchiectasis of the proximal medium-sized bronchi due to allergic bronchopulmonary aspergillosis.

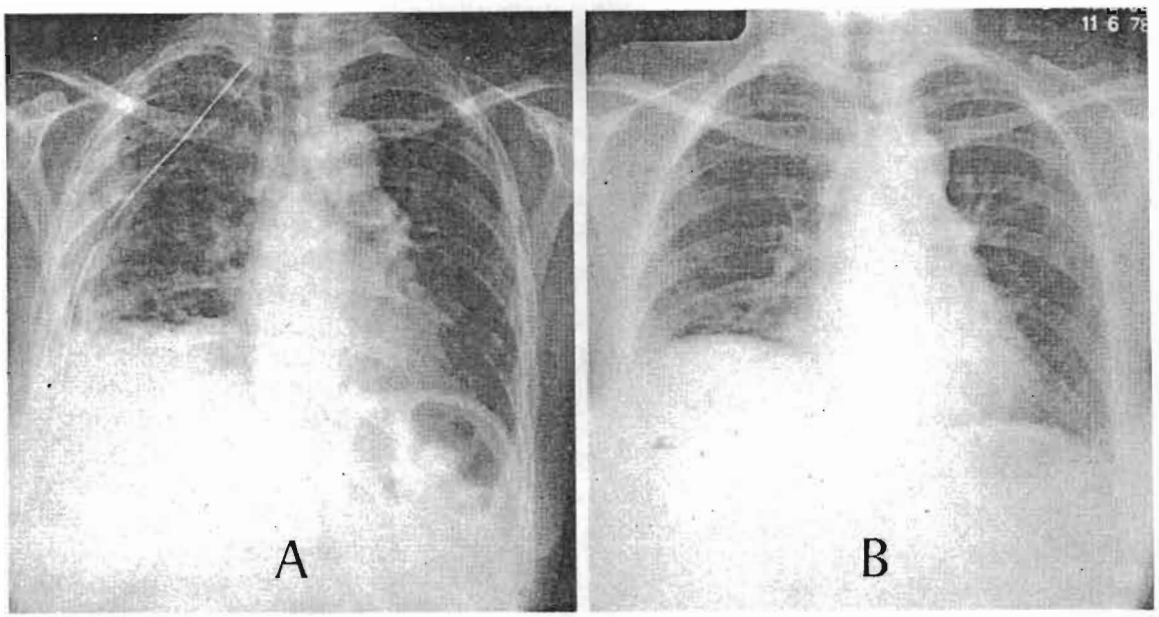

Fig. 4 A Bilateral nodular and linear infiltrate in a young woman with bronchocentric granulomatosis.
B Chest radiograph cleared after corticosteroid therapy.

trations and plasma cells surrounded by palisading epithelioid cells. In some instances, foreign body giant cells are found.[5]

While bronchocentric granulomatosis is well defined pathologically, it is difficult to diagnose clinically. In cases of bronchocentric granulomatosis, unlike in Wegener's granulomatosis, vasculitis is not a prominent feature and veins are not involved. Chondritis is present when larger bronchi are involved.

Bronchocentric granulomatosis may occur in both atopic and nonatopic individuals. Atopic patients are younger; they have eosinophilia and their mucous plugs contain hyphae. The nonatopic patients are a much more heterogeneous group.

Although immunologic mechanisms are not clearly defined in bronchocentric granulomatosis, it seems that the basic abnormality is a hypersensitivity reaction to fungal organisms. Serum precipitating antibodies (IgG) are found in about 40 per cent of the atopic patients.

Corticosteroids are useful in treating patients with bronchocentric granulomatosis who also have asthma. The prognosis is not as favourable in those patients who are nonatopic and who have bronchocentric granulomatosis. It should be remember that little data are available on this disease (Figs. 4A, B).

SAPROPHYTIC COLONIZATION

Aspergilloma

Although the aspergilloma, also known as mycetoma or fungus ball, is considered to be the most common form of an *Aspergillus*-related clinical syndrome, there is little epidemiologic information available on any of these syndromes. *A. fumigatus, A. niger* and other species of *Aspergillus* may colonize old stable pulmonary tubercular cavities, emphysematous bullae, bronchiectatic lesions and lung cysts. Patients who develop such aspergillomas are usually nonatopic.

The diagnosis of aspergilloma is based on chest radiographic findings of a movable, homogeneous opacity inside a cavitary lesion (Figs. 5A, B). The opacity is usually surrounded by an air crescent. The lesions may be single or multiple and there may be calcification within lesions.

Serum precipitating antibodies (IgG) are initially present in high concentrations but become weaker, and assays even become negative, if the fungus ball is taken out. In most cases, the lesion is not invasive. Surgery is indicated when aspergilloma causes life-threatening haemoptysis. Asymptomatic patients do not require any therapy.[6-8]

INVASIVE ASPERGILLOSIS

Invasive, or infective, pulmonary aspergillosis is the second most common mycosis in immunosuppressed patients. Only that caused by *Candida* is more frequently encountered.

Invasive pulmonary aspergillosis usually begins as a necrotizing pneumonitis. Once the fungal organisms enter the blood stream, they produce multiple abscesses in distant organs, including the kidneys and the myocardium. The following presenting forms of invasive pulmonary aspergillosis often occur together, but may also be seen independently.[9,10]

Aspergillus pneumonia

The clinical picture resembles any acute bacterial pneumonia. Fever, dyspnoea, cough and chest pain are common symptoms. Initially, the

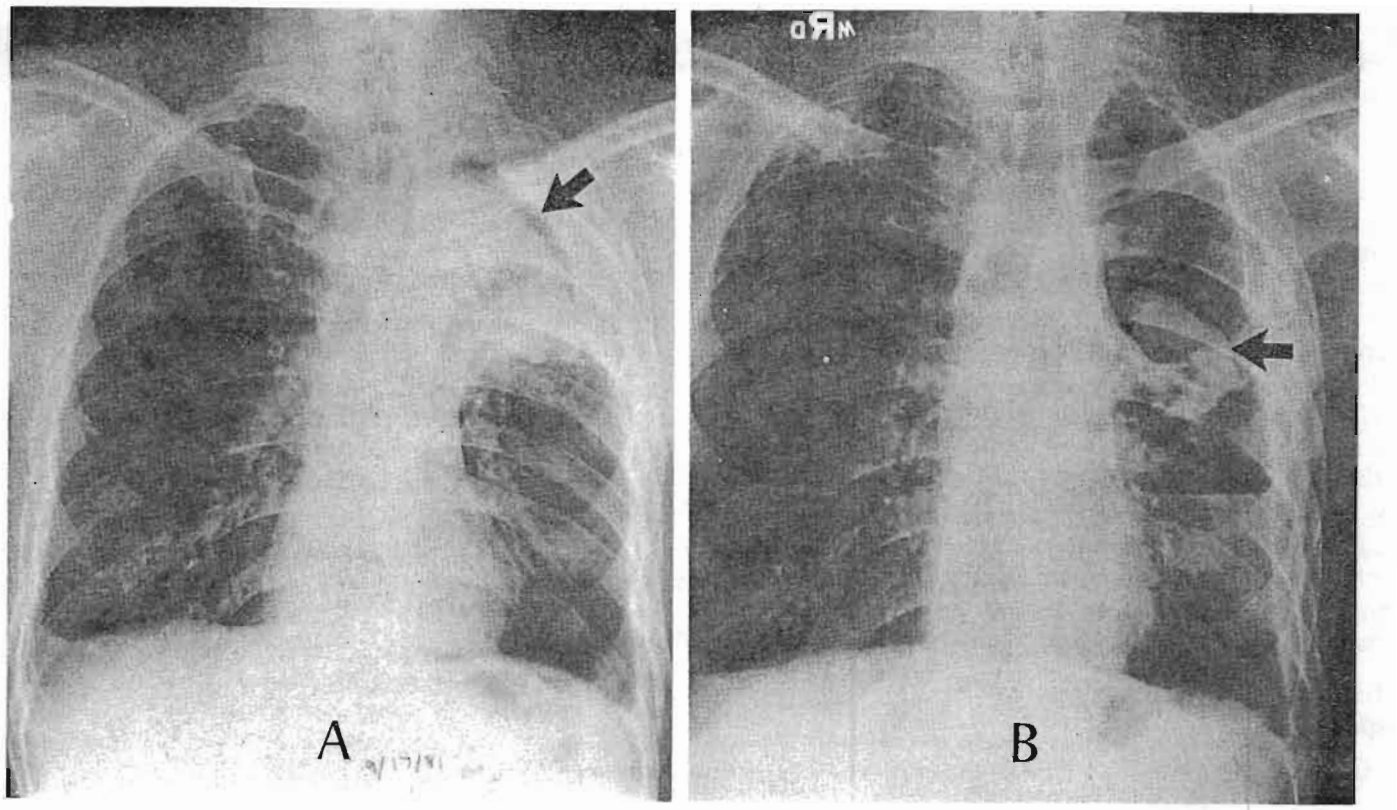

Fig. 5 A Fungus ball in the left upper lung field in a cavity. Note the 'crescent sign' due to the presence of air in the cavity. The 'fungus ball' lies freely in the cavity.

B Fungus ball in the left mid lung field. Note the extensive pleural thickening on the left side.

chest radiograph shows only a patchy infiltrate, which progresses to dense consolidation involving one or both lungs. Despite such an extensive disease process, only 10 per cent of patients have sputum cultures that are positive for *Aspergillus*. To make the definitive diagnosis, parenchymal invasion of lung tissue must be demonstrated.

Lung abscess and multiple cavities

The lung abscess may be focal, resulting from a patch of fungal pneumonia. Disseminated haematogenous spread causes numerous micro-abscesses or cavities. The prognosis is poor; eight out of ten patients with disseminated disease die of septicaemia. Amphotericin B is the only effective therapy.

Aspergillus bronchitis

This is a localized form of airway disease characterized by erosions, ulcers and black membrane formation. Dyspnoea and wheezing are the common symptoms. Haemoptysis occurs in more than half of these patients. Sputum production is scanty.

Infarction

Sometimes vascular invasion by *Aspergillus* causes thrombosis and necrosis resembling pulmonary infarction. The symptoms are episodic and include intense pleuritic chest pain, sudden dyspnoea, tachycardia, gallop rhythm and haemoptysis (in some cases). In about 30 per cent of the patients chest radiographs are normal if they are obtained on the day of the onset of symptoms. If obtained later, the chest film may show a triangular or oval infiltrate, with or without pleural effusion.

Pleural effusion and empyema

This is a rare manifestation. The diagnosis of invasive (infective) aspergillosis should be entertained in the differential diagnosis of fever, pulmonary infiltrate, cavitation or pleural effusion in an immunosuppressed patient. Since sputum and blood cultures are helpful only in a small number of patients, the diagnosis should be established by bronchial brushing and biopsy, using a fibreoptic bronchoscope and percutaneous transthoracic needle biopsy, and an open lung biopsy.

The standard *Aspergillus* precipitating antibodies by gel diffusion are either absent or present in low titres. Newer tests, including counter immuno-electrophoresis, enzyme-linked immunosorbent and passive haemagglutination assay have been correctly positive in 80 per cent of patients. To make the definitive diagnosis of invasive pulmonary aspergillosis, parenchymal invasion of lung tissue must be demonstrated by a lung biopsy. The bronchial brushings, washings, or

sputum that yield *Aspergillus* in culture provide only presumptive evidence of invasive pulmonary aspergillosis.

The mortality rate in cases of invasive aspergillosis is 80 per cent or more. Amphotericin B in high dosage is the only effective therapy. However, 5-fluorocytosine has been used with some success in conjunction with amphotericin B, and experimental studies suggest a synergistic effect between amphotericin B and rifampicin against *Aspergillus*. Serial determinations of anti-*Aspergillus* precipitating antibody titres by enzyme-liked immunosorbent and passive haemagglutination assay techniques may serve as a useful tool for monitoring the course of invasive pulmonary aspergillosis.

Chronic necrotizing pulmonary aspergillosis

Chronic necrotizing pulmonary aspergillosis is defined as an indolent, cavitating process in the lungs due to invasion of lung tissue by the fungus. Binder *et al.* have reviewed 22 cases collected from the literature and added four of their cases, bringing the total number of reported cases to twenty-six.[11] Patients are usually middle-aged, showing indications of immune suppression as evidenced by diabetes mellitus, malnutrition, corticosteroid therapy, radiation therapy and connective tissue diseases. Fever and productive cough are almost always present. Chest radiographs show a patchy pneumonic infiltrate with a cavity. The lesion may be mistakenly diagnosed as tuberculosis or chronic necrotizing pneumonia due to an anaerobic infection. Diagnosis is established by pathologic evidence of tissue invasion by *Aspergillus*. Species precipitating (IgG) antibodies for *Aspergillus* are present. The treatment includes antifungal chemotherapy with surgical resection.

TOXIC PNEUMONITIS

"Mycotoxicosis" is the term used to define the toxic reaction caused by ingestion of the chemical toxins produced by fungi. As many as 64 toxic metabolites are found in the genus *Aspergillus*. Inhalation exposure to these toxins may occur in various industries, agricultural surroundings, breweries, textile mills, oil processing plants and grain storage facilities. Although most physicians are familiar with extrinsic allergic alveolitis produced by inhalation of organic particles, the toxic effects of fungi have not been widely appreciated.

The clinical picture of mycotoxicosis consists of acute illness with fever, dry cough, dyspnoea, and nasal and conjunctival injection. Chest radiographs usually reveal diffuse interstitial infiltration involving mostly the lower two-thirds of both lungs.[12]

Lung biopsy specimens show interstitial pneumonitis with neutrophils, lymphocytes and histiocytes, but not granulomata. This histologic picture is very different from that seen in extrinsic allergic alveolitis. Immunologic studies show no evidence of hypersensitivity to fungal antigens.

Corticosteroids are the treatment of choice in severe cases, in which hypoxia and ventilatory failure complicate the picture. Although one (and only one) thorough case report indicates that *Aspergillus* may cause mycotoxicosis, more studies are needed to determine the nature of fungal toxins and pathogenetic mechanisms involved in the genesis of this syndrome.

Summary

Aspergillus causes a wide variety of disorders ranging from allergic asthma to fatal infections. The most common problems are aspergillomas, or fungus balls, which grow in existing cavities of the lung. In the U.S.A. allergic asthma and allergic bronchopulmonary aspergillosis occur primarily in atopic persons between October and February. Extrinsic allergic alveolitis is an occupational illness of nonatopic persons who work with vegetable matter, usually barley. Invasive, or infective, aspergillosis strikes immunosuppressed patients. The only cure for the invasive form of the disease is amphotericin B; however, even with therapy, the mortality rate exceeds 80 per cent.

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