

The Clinical Spectrum of Pulmonary Aspergillosis*

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Aspergillus is a ubiquitous fungus that causes a variety of clinical syndromes in the lung, ranging from aspergilloma in patients with lung cavities, to chronic necrotizing aspergillosis in those who are mildly immunocompromised or have chronic lung disease. Invasive pulmonary aspergillosis (IPA) is a severe and commonly fatal disease that is seen in immunocompromised patients, while allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to Aspergillus antigens that mainly affects patients with asthma. In light of the increasing risk factors leading to IPA, such as organ transplantation and immunosuppressive therapy, and recent advances in the diagnosis and treatment of Aspergillus-related lung diseases, it is essential for clinicians to be familiar with the clinical presentation, diagnostic methods, and approach to management of the spectrum of pulmonary aspergillosis.

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Key words: allergic pulmonary aspergillosis; Aspergillus; fungal diseases; immunocompromised host; pulmonary infection

Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; BMT = bone marrow transplantation; CNA = chronic necrotizing aspergillosis; IPA = invasive pulmonary aspergillosis

Aspergillus is a ubiquitous soil-dwelling organism found in organic debris, dust, compost, foods, spices, and rotted plants. There are approximately 200 species of Aspergillus; however, only a few are known to be pathogenic for humans. *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger* are the most commonly encountered species, but other species, like *Aspergillus terreus*, *Aspergillus clavatus*, *Aspergillus niveus*, and *Aspergillus nidulans*, have rarely been reported to cause disease in humans.¹

Aspergillus, like other filamentous fungi, is primarily acquired from an inanimate reservoir, usually by the inhalation of airborne spores. The organism grows best at 37°C, and the small spores (2 to 3 µm) are easily inhaled and deposited deep in the lungs, leading to a variety of clinical syndromes (Fig 1). Although these are distinct pulmonary entities, on rare occasions one condition may change to another; for example, an aspergilloma may change to invasive pulmonary aspergillosis (IPA).^{2,3}

This article reviews the clinical spectrum of pulmonary aspergillosis, emphasizing the risk factors, clinical picture, and recent advances in diagnostic and therapeutic approaches.

ASPERGILLOMA

This is the most common and best-recognized form of pulmonary involvement due to Aspergillus. The aspergilloma (fungal ball) consists of masses of fungal mycelia, inflammatory cells, fibrin, mucus, and tissue debris, usually developing in a preformed lung cavity. Although other fungi may cause the formation of a fungal ball (for example, *Zygomycetes* and *Fusarium*), Aspergillus spp (specifically, *A fumigatus*) are by far the most common etiologic agents.

The true incidence of aspergilloma is not known. In a study⁴ of 544 patients with pulmonary cavities secondary to tuberculosis, 11% had radiologic evidence of aspergilloma. The most common predisposing factor is the presence of a preexisting lung cavity formed secondary to tuberculosis, sarcoidosis, bronchiectasis, bronchial cysts and bullae, ankylosing spondylitis, neoplasm, or pulmonary infarction.^{5,6} Of these, tuberculosis is the most frequently associated condition.⁷ Occasionally, aspergilloma has been described in cavities caused by other fungal infections.^{8,9} It is believed that inadequate drainage facilitates the growth of Aspergillus on the walls of these cavities.

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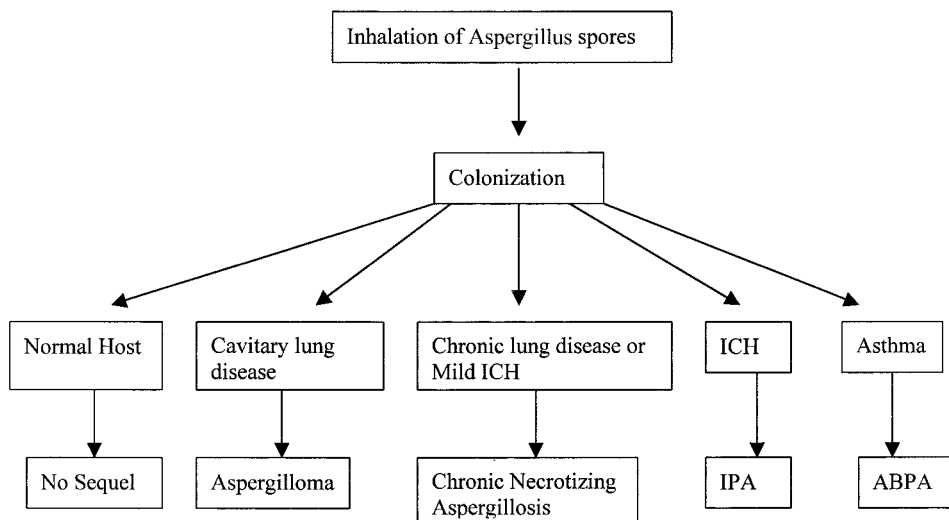


FIGURE 1. The clinical spectrum of conditions resulting from the inhalation of *Aspergillus* spores. ICH = immunocompromised host.

Usually, the fungus does not invade the surrounding lung parenchyma or blood vessels; exceptions, however, have been noted.^{2,10}

The natural history of aspergilloma is variable. In the majority of cases, the lesion remains stable, however, in approximately 10% of cases, it may decrease in size or resolve spontaneously without treatment.¹¹ Rarely, the aspergilloma increases in size.¹²

Clinical Picture

An aspergilloma may exist for years without causing symptoms. Most patients will experience mild hemoptysis, but severe hemoptysis may occur, particularly in patients with underlying tuberculosis.¹³ Bleeding usually occurs from bronchial blood vessels. Theories on the cause of the hemoptysis include local invasion of blood vessels lining the cavity, endotoxins released by the fungus with hemolytic properties, and mechanical friction of the aspergilloma with the cavity wall blood vessels.^{2,14,15} The mortality rate from hemoptysis ranges between 2% and 14%.^{16–20} Other symptoms include chronic cough and dyspnea that are probably more related to the underlying lung disease. Fever is rare unless there is secondary bacterial infection.

Risk factors associated with poor prognosis of aspergilloma are severe underlying disease, increasing size or number of lesions as seen on chest radiographs, immunosuppression (including corticosteroid treatment), increasing *Aspergillus*-specific IgG titers, recurrent large-volume hemoptysis, and underlying sarcoidosis or HIV infection.²¹

Diagnosis

Aspergilloma usually comes to clinical attention as an incidental finding on a routine chest radiograph or during an evaluation of hemoptysis. Radiologically, aspergilloma is evident as an upper-lobe, mobile, intracavitary mass with an air crescent in the periphery.²² The adjacent pleura may be thickened. At times, the mass may be difficult to see on a routine chest radiograph, and tomography or chest CT scan may be necessary to visualize the aspergilloma²³ (Fig 2). A change in the position of the aspergilloma with a change of position of the patient is an interesting but variable sign.²³ The differential diagnosis of this radiologic appearance includes hematoma, neo-

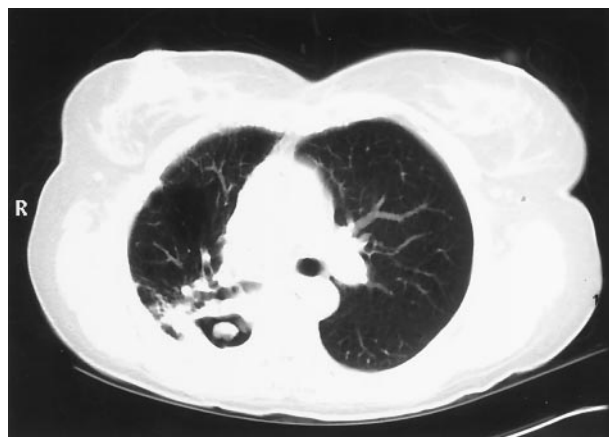


FIGURE 2. Chest CT scan of a patient with a history of lung cancer and tuberculosis, who developed aspergilloma after undergoing resection of the right upper lobe.

plasm, abscess, hydatid cyst, and Wegener granulomatosis. It is important to note that aspergilloma may coexist with any of the above conditions.^{24,25}

A sputum examination may reveal the presence of *Aspergillus* but is negative in 50% of the cases.²⁶ Serum IgG antibodies to *Aspergillus* are positive in almost all cases; however, they may be falsely negative in the rare cases of aspergilloma due to species other than *A. fumigatus* or in patients receiving corticosteroid therapy.¹⁰ Immediate skin reactivity is much less helpful in the evaluation of aspergilloma and is positive only in a minority of patients.²⁶

Treatment

In asymptomatic patients, no therapy is warranted. There is no consistent evidence that aspergilloma responds to antifungal agents, and these drugs rarely achieve the minimal inhibitory concentrations within the lung cavities.²⁷ Inhaled, intracavitary, and endobronchial instillations of antifungal agents have been tried with no consistent success.^{19,28,29} In addition, systemic antifungal therapy using IV amphotericin B failed to show a benefit in patients with aspergilloma.³⁰ Itraconazole therapy has been tried with variable results.³¹⁻³³ Bronchial artery embolization rarely results in control of hemoptysis because of the massive collateral blood vessels; however, this procedure should be considered as a temporizing measure in patients with life-threatening hemoptysis.³⁴ The surgical treatment of aspergilloma is associated with relatively high mortality rate that ranges between 7% and 23%.^{15-17,35-38} The most common causes of death following surgery are severe underlying lung disease, pneumonia, acute myocardial infarction, and IPA.^{19,38} In addition, there is significant postoperative morbidity, including bleeding, residual pleural space, bronchopulmonary fistula, empyema, and respiratory failure. A recent report³⁹ of 87 patients who were operated on for pulmonary aspergilloma revealed a postoperative mortality rate of 5.7%. Another report³⁸ showed a lower mortality rate of 1.5% and morbidity of 18% in the surgical treatment of aspergilloma; however, most of the patients were young with adequate respiratory reserve, and tuberculosis was the underlying lung disease in the vast majority of the patients.

In summary, observation alone is adequate in most cases of aspergilloma. Medical therapy with bed rest, humidified oxygen, cough suppressants, and postural drainage is helpful in cases of mild hemoptysis. The surgical approach needs to be considered in patients with massive hemoptysis and adequate pulmonary reserves.²⁰ The role of itraconazole is yet to be determined.

CHRONIC NECROTIZING ASPERGILLOSIS

Also called semi-invasive aspergillosis, this entity was first described in two reports in 1981 and 1982.^{40,41} Chronic necrotizing aspergillosis (CNA) is an indolent, destructive process of the lung due to invasion by *Aspergillus* species (usually *A. fumigatus*). This entity is different from aspergilloma in that there is local invasion of the lung tissue, and a preexisting cavity is not needed, although a cavity with a fungal ball may develop in the lung as a secondary phenomenon due to destruction by the fungus. On occasion, an aspergilloma may invade the cavity wall, causing local parenchyma destruction, as seen in patients with CNA.⁴² CNA is also different from invasive aspergillosis. The former, in contrast to the latter, is a chronic process that progresses slowly over months to years, and there is no vascular invasion or dissemination to other organs.⁴⁰

CNA is usually seen in middle-aged and elderly patients with documented or suspected underlying lung diseases like COPD, inactive tuberculosis, previous lung resection, radiation therapy, pneumoconiosis, cystic fibrosis, lung infarction, or, rarely, sarcoidosis.⁴³ It also has been described in patients with mild immunosuppression, including those with diabetes mellitus, those with poor nutrition, those undergoing low-dose corticosteroid therapy, and those with connective tissue diseases such as rheumatoid arthritis and ankylosing spondylitis.⁴⁰

The patient usually presents with fever, cough, sputum production, and weight loss of 1 to 6 months' duration. A minority of the patients may be asymptomatic.⁴⁰ The chest radiograph usually shows an infiltrative process in the upper lobes or the superior segments of the lower lobes. A fungal ball may be seen in nearly one half of the cases.⁴⁰ Adjacent pleural thickening is a characteristic finding and may be an early indication of a locally invasive process.⁴¹

The diagnosis is confirmed by a histologic demonstration of tissue invasion by the fungus and the growth of *Aspergillus* species on a culture. However, the yield of transbronchial biopsy specimens or percutaneous aspirates is relatively poor, and a thoracoscopic or open-lung biopsy is rarely performed in these patients. So, a clinical diagnosis of CNA could be made using the following criteria:

- Clinical and radiologic features consistent with the diagnosis;
- Isolation of *Aspergillus* species by culture from sputum or from bronchoscopic or percutaneous samples; and
- Exclusion of other conditions with similar presentations, such as active tuberculosis, atypical mycobacterial infection, chronic cavitary histoplasmosis, or coccidioidomycosis.

Other helpful but nondiagnostic tests include serum IgG antibodies to *Aspergillus* (positive results in > 90% of the patients) and immediate skin reactivity for *Aspergillus* antigens.

Treatment with antifungal medications is indicated once the diagnosis is made. The response to therapy with IV amphotericin B is generally favorable.^{40,42} However, therapy with itraconazole has emerged as an effective alternative to the relatively toxic amphotericin B.^{42,44} Surgical resection is generally reserved for healthy young patients with focal disease and good pulmonary reserves, patients not tolerating antifungal therapy, and patients with residual localized but active disease despite adequate antifungal treatment. In the initial series by Binder et al,⁴⁰ 90% of patients who underwent surgical resections had good responses. However, there were significant postoperative complications, and one patient died.⁴⁰

The long-term prognosis for patients with CNA is not well-documented. In the original series,⁴⁰ 73% of the patients were alive 1 to 2 years following therapy, and the majority of deaths was due to other causes.

IPA

The incidence of IPA has been on the rise since it was first described in 1953.⁴⁵ Groll et al⁴⁶ documented a rise in the rate of invasive mycoses from 0.4 to 3.1% of all autopsies performed between 1978 and 1992. In addition, invasive aspergillosis increased from 17% of all mycoses found on autopsy at the beginning of the study to 60% at the end of the 14-year study period.

The vast majority of IPA cases are seen in immunocompromised patients. The risk factors are summarized in Table 1.^{47–51} Neutropenia is the most important risk factor, and it is estimated that IPA accounts for 7.5% of all infections in neutropenic patients following induction therapy for acute myelogenous leukemia.⁴⁷ The risk of IPA increases with the duration of neutropenia (*ie*, neutrophil count, < 500 cells/ μ L) and is estimated to be 1% per day for the first 3 weeks, after which time it increases to 4% per day.⁴⁷ Transplantation, especially lung and

bone marrow transplantation (BMT), is another increasingly significant risk factor for IPA.⁵² It is estimated that 5% of BMT recipients develop IPA with mortality rates ranging between 30% and 80%.^{53–55} In BMT recipients, IPA may be seen in the first few weeks after the procedure with delayed engraftment or graft failure, and more commonly in the setting of treatment with corticosteroids for graft-vs-host disease. The increased risk of IPA in patients undergoing transplantation is related to multiple immune defects including prolonged neutropenia in the pre-engraftment phase of BMT, and the use of multiple antirejection or anti-graft-vs-host disease therapy, including corticosteroids and cyclosporine. In addition, other factors that predispose patients to fungal infections in general, such as parenteral nutrition, use of multiple antibiotics, and prolonged hospitalization, increase the risk of IPA following transplantation. IPA also has been reported increasingly in patients with HIV infection.⁵¹ While most HIV-infected patients have the same risk factors for *Aspergillus* infection as those in other patient populations (such as patients with neutropenia and those receiving corticosteroid therapy), there are a growing number of reports of IPA in AIDS patients without the traditional risk factors.^{56,57} Besides the usual clinical picture of IPA, there is increased incidence of tracheobronchial involvement.⁵⁸ The response to therapy is particularly poor in the HIV-infected population.⁵¹

Rarely, IPA has been reported^{59,60} in apparently immunocompetent patients or in those individuals who are mildly immunocompromised, such as patients with alcoholism, chronic liver disease, or diabetic ketoacidosis. In addition, IPA is increasingly recognized in patients with advanced COPD, especially those treated with oral corticosteroids.^{61,62} In a recent review⁶³ of 545 patients with invasive aspergillosis, BMT was the most frequent risk factor (32%; autologous BMT, 7%; allogeneic BMT, 25%), followed by hematologic malignancy (29%), solid organ transplantation (9%), and AIDS (8%). In 2% of patients, no underlying risk factors were identified.

Clinical Picture

The lower respiratory tract is almost always the primary focus of infection as a result of the inhalation of the infectious spores. Less commonly, IPA may start in locations other than the lungs, like the sinuses, the GI tract, or the skin (*ie*, resulting from the insertion of IV catheters, prolonged skin contact with adhesive tapes, or burns).^{64–67}

Consequently, patients usually present with respiratory symptoms that are consistent with bronchopneumonia, with fever, cough, sputum production,

Table 1—Major Risk Factors for IPA

1. Prolonged neutropenia (> 3 wk) or neutrophil dysfunction (chronic granulomatous disease)
2. Corticosteroid therapy (especially prolonged, high-dose therapy)
3. Transplantation (highest risk is with lung and bone marrow)
4. Hematologic malignancy (risk is higher with leukemia)
5. Cytotoxic therapy
6. AIDS (risk increases with lower CD4 count)

and dyspnea. Two other symptoms that are significant and that raise the possibility of IPA in the appropriate clinical setting are pleuritic chest pain (due to small pulmonary infarctions secondary to vascular invasion) and hemoptysis that is usually mild but could be massive. IPA is one of the most common causes of hemoptysis in neutropenic patients; and has been reported to be associated with cavitation that occurs with neutrophil recovery.⁶⁸ Other pulmonary manifestations include isolated tracheobronchitis with severe inflammation of the airways that is associated with ulcerations and plaque formation. This may lead to airway obstruction and secondary atelectasis. This form of IPA has been most commonly reported in patients with AIDS and in lung transplant recipients.^{69,70}

With the predilection of *Aspergillus* to invade blood vessels, IPA commonly leads to areas of infarction and hemorrhage in the primary organ (usually the lungs), and the organism spreads hematogenously to other organs, most commonly the brain (leading to seizures, ring-enhancing lesions, cerebral infarctions, intracranial hemorrhage, meningitis, and epidural abscess), and less commonly skin, kidneys, pleura, heart, esophagus, liver, or any other site.⁷¹

Diagnosis

The diagnosis of IPA is difficult. A high index of suspicion is necessary in patients with risk factors for invasive aspergillosis. The diagnosis is best made by demonstrating the presence of septate, acute, branching hyphae in the lung tissue sample along with a culture that is positive for *Aspergillus* from the same site. Methenamine-silver and periodic acid-Schiff stains are the usual stains to demonstrate the characteristic hyphae. Other fungi such as *Fusarium* and *Scedosporium* may have similar appearances, thus increasing the importance of performing a culture for the accurate identification of the fungus.

The presence of the *Aspergillus* species in sputum samples could be due to colonization of the airway; however, in the immunocompromised patient sputum culture positivity may be the only indication of IPA. Studies⁷²⁻⁷⁴ have shown that sputum samples that are positive for *Aspergillus* in patients with leukemia or in those who have undergone BMT have a positive predictive value of 80 to 90%. On the other hand, a sputum sample that is negative for *Aspergillus* does not exclude the diagnosis of IPA, since negative sputum studies have been noted in 70% of patients with confirmed IPA.⁷⁵ Blood cultures rarely have positive results.⁷⁶

The chest radiograph often shows nonspecific changes. The lesions that are suggestive of IPA

include rounded densities, pleural-based infiltrates that are suggestive of pulmonary infarctions, and cavitation. Pleural effusions are uncommon.^{77,78} The chest CT scan, especially with high-resolution images, is a much more helpful tool in the diagnosis of IPA. It leads to earlier diagnosis, and aids further diagnostic studies like bronchoscopy and open-lung biopsy.^{79,80} The routine use of high-resolution chest CT scans in patients with suspected IPA has been associated with better outcomes, probably due to earlier diagnosis. Of the 156 patients who underwent chest CT scans in the report by Patterson et al,⁶³ 85% had findings that were suggestive of IPA. Typical chest CT scan findings are multiple nodules (Fig 3), the halo sign, which is an early radiologic sign that appears as a zone of low attenuation due to hemorrhage surrounding the pulmonary nodule,⁸¹ and the air crescent sign, which is a crescent-shaped lucency in the region of the original nodule secondary to necrosis.⁸² The air crescent sign usually correlates with recovery from neutropenia and is a relatively late sign.⁸³ The last two radiologic signs are relatively specific for IPA, but they are neither sensitive nor pathognomonic; other infections like nocardiosis and zygomycoses may have a similar appearance.^{81,82}

BAL is helpful in the diagnosis of IPA, especially in patients with diffuse lung involvement. The BAL fluid is tested by fungal smear and culture. The specificity of a positive result of BAL fluid testing is very high, reaching 97%,⁸⁴ but the sensitivity is reported to be approximately 30 to 50%.^{84,85} Transbronchial biopsies have not been shown to add much to the results of BAL and are associated with increased risks.¹⁹ Open or thoracoscopic lung biopsies are generally the "gold standard" in the diagnosis of

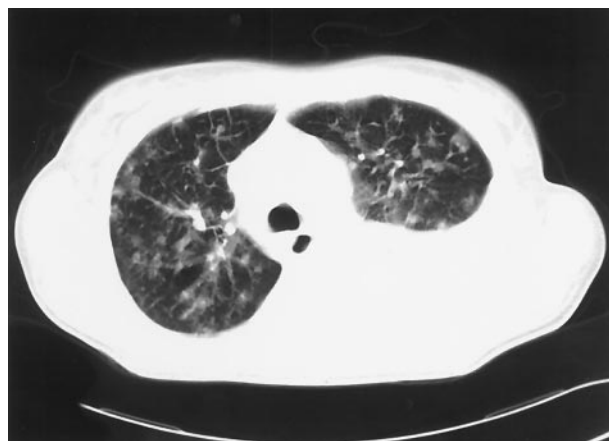


FIGURE 3. Chest CT scan of a patient with chronic lymphocytic leukemia and histologically proven IPA showing multiple pulmonary nodules.

pulmonary problems in immunocompromised patients; however, in the case of IPA, this procedure is known to be associated with false-negative results. In a study⁸⁶ of 15 patients who had undergone open-lung biopsies, the presence of IPA was missed in 3. Thus, open-lung biopsy is reserved for patients in whom the diagnosis of IPA remains uncertain despite results from the mentioned studies, and when such a procedure is expected to have an impact on the patients' management and outcome.

Serology has not been useful in the diagnosis of IPA. Aspergillus antibody detection is not useful, probably due to the poor immune response of patients with IPA and the rapidity with which the infection occurs, not giving enough time for an adequate antibody response.⁸⁷

There has been increasing interest in Aspergillus antigen detection from serum and BAL samples. Some studies⁸⁸ suggest that antigenemia may be detected before the presence of clinical features of IPA. A sandwich enzyme-linked immunosorbent assay technique that utilizes monoclonal antibodies to galactomannan (*ie*, the cell wall glycoprotein that binds lectin) has been developed to detect the Aspergillus antigen in serum, urine, and BAL fluid and has a reported sensitivity and specificity of > 90%.^{88–92} This method, while commercially available in Western Europe, has not yet been approved in the United States.

Polymerase chain reaction is another experimental method with which to diagnose IPA by the detection of Aspergillus DNA in BAL fluid and serum. The extrasensitive nature of this method and the ubiquitous presence of the fungus create a high likelihood of false-positive results.^{93,94}

The National Institute of Immunology, Allergy, and Infectious Diseases has provided a working case definition. The diagnosis of IPA is definite when tissue histopathology shows the hyphae, with or without a positive culture for Aspergillus from the same site, or a positive culture from tissue obtained by an invasive procedure such as trans-bronchial biopsy, percutaneous needle aspiration, or open-lung biopsy. The diagnosis of IPA is probable when the clinical picture is consistent with the diagnosis, and when two sputum cultures or one BAL fluid culture, a bronchial washing culture, or a brushing culture for Aspergillus species, or a cytologic examination of the BAL fluid shows the characteristic hyphae or positive Aspergillus antigen in the serum or BAL fluid. The diagnosis is possible when the clinical picture is compatible without documentation of any mycologic evidence of IPA.^{63,95}

Treatment

The treatment of IPA is difficult, and the mortality rate remains high despite recent advances in therapy. Empiric therapy should be started as soon as there is clinical suspicion of IPA, and while a workup is underway. The outcome of therapy is dependent on an early diagnosis, the absence of dissemination, the instigation of intensive antifungal therapy, and the recovery of the underlying host defense defect, such as the resolution of neutropenia or the tapering of immunosuppression therapy.^{96–98} In the review by Patterson et al,⁶³ patients who had severe immunosuppression, such as those who had undergone BMT and had hematologic malignancy, had poor responses to therapy compared to less severely immunosuppressed patients (28% vs 51%, respectively). Also, when IPA was limited to the lung, the response was better than in patients with disseminated infection (40% vs 18%, respectively). The most widely used drug in the treatment of IPA is amphotericin B. Its usual dose is 0.6 to 1.2 mg/kg/d; however, higher doses (*ie*, 1 to 1.5 mg/kg/d) may be necessary in severely immunocompromised patients with overwhelming infections.⁹⁹ The optimal duration of antifungal drug therapy is not known, but treatment is recommended to continue past the period of immunosuppression and until the disease appears to be clinically resolved.¹⁹ Even with optimal therapy, the response rate varies widely between 20% and 83%.¹⁰⁰

Amphotericin B is known to cause serious side effects such as nephrotoxicity, electrolyte disturbances, and hypersensitivity reactions. Newer lipid-based preparations of amphotericin B (*eg*, liposomal amphotericin B and lipid complex amphotericin B) have been introduced in an effort to minimize these side effects. These preparations enable the administration of higher doses of amphotericin B with less toxicity and are indicated in patients who are at high risk for nephrotoxicity, who develop toxicity while receiving amphotericin B, or who respond poorly to that medication.^{19,101–104}

Itraconazole, a triazole, is another agent that is used in the treatment of IPA, in doses of 200 to 400 mg/d.^{30,105} The drug is available in oral (*ie*, capsule and suspension) and IV formulations. The itraconazole capsule should be avoided in the treatment of IPA in view of its poor bioavailability. In a large nonrandomized study,⁹⁵ itraconazole was found to result in complete or partial response in 39% of patients with IPA, and in a failure to respond to treatment in 26%. The results were particularly poor in allogeneic BMT recipients and AIDS patients. It is reasonable to consider therapy with itraconazole as an alternative to that with amphotericin B in patients

with IPA who are less immunocompromised and in the late stages of therapy after the initial control of the infection with amphotericin B therapy. Because of drug-drug interactions, itraconazole needs to be used with caution. The use of combination therapy (for example, amphotericin B with 5-fluorocytosine, rifampin, itraconazole, or ketoconazole) has not been shown to be more effective in the treatment of patients with IPA.¹⁰⁶ Trials¹⁹ are currently underway testing several new promising drugs like voriconazole, posaconazole, and echinocandin derivatives. Caspofungin, an echinocandin derivative was recently approved¹⁰⁷ for the treatment of IPA in patients with refractory infection or those intolerant to conventional therapy.

Other modalities of therapy include surgical resection, which should be considered in cases of massive hemoptysis,¹⁰⁸ or the resection of residual localized pulmonary lesions in patients with continuing immunosuppression or those who are expected to have further immunosuppressive therapy in the future.¹⁰⁹ Surgery has been performed safely in selected neutropenic patients.^{109–111} The surgical outcome is poor in patients with multiple foci of infection, in those who have undergone allogeneic BMT, and those requiring mechanical ventilation.

The value of immunomodulatory therapy such as that using cytokines (*ie*, granulocyte colony-stimulating factor, granulocyte macrophage-colony-stimulating factor, or interferon- γ) as adjuvant therapy is not clear, and large studies on the safety and efficacy of these agents are lacking.¹¹²

Given the difficulties in the management of IPA, an important approach to this problem is prophylaxis for those patients who are at increased risk for IPA. Avoiding the hospitalization of patients in areas where there is construction and the use of high-efficiency particulate air or laminar air flow have been shown to decrease the rate of IPA in some studies.¹¹³ Also chemoprophylaxis using low-dose amphotericin B and intranasal amphotericin B have been studied with variable results.^{114,115} Currently chemoprophylaxis trials using itraconazole and posaconazole are underway in allogeneic BMT recipients.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to *Aspergillus* antigens, mostly due to *A fumigatus*. It is typically seen in patients with long-standing asthma or cystic fibrosis, and it is estimated that 7 to 14% of corticosteroid-dependent asthma patients and 6% of patients with cystic fibrosis meet the diagnostic criteria for

ABPA.^{116,117} The factors leading to ABPA are not clearly understood. It is believed that *Aspergillus*-specific, IgE-mediated type I hypersensitivity reactions and specific IgG-mediated type III hypersensitivity reactions play a central role in the pathogenesis of ABPA.^{118,119} Other host factors, including cellular immunity, may contribute to the pathologic changes seen in ABPA.^{120,121} Since the diagnosis of ABPA is usually made on clinical grounds, lung biopsies are rarely performed. In a study¹²² of 18 pathologic specimens from patients with ABPA, the most significant findings involved the bronchi and bronchioles with bronchocentric granulomas in 15 specimens and mucoid impaction in 11. Other findings included granulomatous inflammation with histiocytes and lymphocytes, increased numbers of eosinophils, and exudative bronchiolitis. Fungal hyphae were commonly seen without evidence of tissue invasion.¹²²

Diagnosis

ABPA is usually suspected on clinical grounds, and the diagnosis is confirmed by radiologic and serologic testing. The patient usually presents with wheezing, expectoration of brown mucus plugs, pleuritic chest pain, and fever.¹²³ The chest radiograph findings may be normal in the early stages of the disease. During acute exacerbations, the typical findings are fleeting pulmonary infiltrates that tend to be in the upper lobe and central in location. There may be loss of volume due to mucoid impaction of the airways. This latter manifestation may present as band-like opacities emanating from the hilum with rounded distal margins (gloved finger appearance).¹²⁴ At later stages, central bronchiectasis and pulmonary fibrosis develop. The chest CT scan is more sensitive in demonstrating the above changes. The IgE level serves as a marker for flare-ups and responses to therapy.¹²⁵ A positive sputum culture for *A fumigatus* is not essential for the diagnosis, and indeed in rare cases a syndrome similar to ABPA is triggered by fungi other than *Aspergillus*. Immediate skin reactivity to *A fumigatus* antigens and elevated levels of serum IgG antibodies to *Aspergillus* are usually present.¹¹⁸ Lung biopsy is rarely performed for the diagnosis of ABPA.

Greenberger and Patterson recently modified the diagnostic criteria for ABPA (Table 2).^{123,125} Not all of these criteria need to be present to diagnose ABPA. Withholding therapy until the development of all clinical symptoms and evidence of bronchiectasis may lead to a missed diagnosis in a significant number of patients and to delayed treatment resulting in irreversible pulmonary damage. Therefore, ABPA may be subdivided into the following two

Table 2—Diagnostic Criteria for ABPA

1. Asthma
2. Immediate skin reactivity to *Aspergillus*
3. Serum precipitins to *A fumigatus*
4. Increased serum IgE and IgG to *A fumigatus*
5. Total serum IgE > 1,000 ng/mL
6. Current or previous pulmonary infiltrates
7. Central bronchiectasis
8. Peripheral eosinophilia (1,000 cells/ μ L)

groups: patients with or without central bronchiectasis. The essential criteria for diagnosis of the group with ABPA and central bronchiectasis are asthma, immediate skin reactivity to *Aspergillus* antigens, serum IgE level > 1,000 ng/mL, and central bronchiectasis. Patients without central bronchiectasis are labeled ABPA-seropositive, and the minimal criteria for diagnosis are asthma, immediate skin reactivity to *Aspergillus*, serum IgE level > 1,000 ng/mL, history of pulmonary infiltrates, and elevated levels of serum IgE and IgG antibodies to *A fumigatus*.¹²⁷

Patterson et al¹²⁸ divided this syndrome into five stages that help to guide the management of the disease. It is not necessary for a patient to progress through all of these stages. Stage I (acute stage) is characterized by asthma, a markedly elevated IgE level, peripheral eosinophilia, pulmonary infiltrates, and the presence of IgE and IgG antibodies to *A fumigatus*. In practice, patients are rarely identified in this stage. In stage II (remission stage), the IgE level falls, but not to the normal range, eosinophilia is absent, and the chest radiograph is clear. Serum IgG antibodies to *Aspergillus* may be slightly elevated. Stage III (exacerbation stage) is diagnosed in a patient who is known to have ABPA and is similar to stage I. The IgE level is usually double that at baseline. Stage IV (the corticosteroid-dependent stage) occurs when the patient becomes steroid-dependent and attempts to taper the steroid therapy, resulting in an obvious worsening of symptoms and the development of pulmonary infiltrates. The serum IgE level is usually elevated but may be normal. Frequently, the chest CT scan will show central bronchiectasis. Unfortunately, the syndrome is diagnosed in the majority of patients at this stage.¹²⁹ Stage V (fibrotic stage) is characterized by clinical features of end-stage lung disease with dyspnea, cyanosis, rales, and cor pulmonale. Clubbing may be present. The serum IgE level and eosinophil count may be low or high. A minority of patients progress to this stage.

Treatment

The mainstay of therapy for ABPA is oral corticosteroids to suppress the immunologic response to

Aspergillus antigens and the secondary inflammatory reaction. Treatment with corticosteroids leads to the relief of bronchospasm, the clearing of pulmonary infiltrates, and a decrease in IgE level and peripheral eosinophilia.^{130,131} Oral prednisone is administered at 0.5 mg/kg/d for 2 weeks then gradually is tapered.¹³² The duration of therapy should be individualized according to the patient's clinical condition. Most patients, however, require prolonged low-dose corticosteroid therapy to control their symptoms and minimize relapses.^{132,133} Inhaled steroids are not helpful in preventing the progression of lung damage associated with ABPA.¹³⁴

Since there are side effects associated with long-term corticosteroid therapy, including an increased risk of invasive aspergillosis,¹³⁵ interest in other modalities of treatment of ABPA has developed. Recently, a randomized prospective study¹³⁶ was performed to evaluate the role of an antifungal agent, itraconazole, in the management of ABPA. The study showed that 46% of patients treated with itraconazole, 200 mg bid for 16 weeks, had a significant response, which was defined as a 50% reduction in the corticosteroid dose, a decrease of at least 25% in the serum IgE concentration, and a 25% improvement in exercise tolerance or pulmonary function test results, or the resolution or absence of pulmonary infiltrates. There was no significant toxicity related to this therapy. The study concluded that patients with ABPA generally benefit from concurrent itraconazole therapy and suggested that a lower dose of itraconazole (200 mg daily) was equally beneficial and may be useful as a maintenance therapy to sustain remission.

Syndromes Related to ABPA

Mucoid Impaction: This feature of ABPA may be seen without asthma or other features of the disease. The patient usually presents with a cough and expectoration of mucus plugs.¹³⁷ The mucus plugging may lead to atelectasis, which may arouse suspicion of endobronchial malignancy.¹³⁸

Bronchocentric Granulomatosis: This syndrome is characterized by necrotizing granulomas that obstruct and destroy the bronchioles. The *Aspergillus* hyphae are identified within the granulomas in 40 to 50% of patients with bronchocentric granulomatosis.⁹⁹ The lung parenchyma is marked by the presence eosinophilic inflammatory infiltrates and fibrosis, however, there is no tissue or vascular invasion by the *Aspergillus*. Clinically, the patients are almost always asthmatic and have a persistent cough with peripheral eosinophilia and increased serum IgE levels. The chest radiograph usually shows solitary or

multiple pulmonary nodules that may be mistaken for malignancies. The patients usually respond to corticosteroid therapy.¹³⁹

Eosinophilic Pneumonitis: Aspergillus rarely has been implicated in the etiology of this syndrome. The patient usually presents with cough, dyspnea, and fever associated with peripheral pulmonary infiltrates, and an elevation of Aspergillus IgE levels. The diagnosis usually is confirmed by biopsy, and patients respond well to corticosteroid therapy.^{140,141}

Hypersensitivity Pneumonitis: Also known as extrinsic allergic alveolitis, it is a form of hypersensitivity granulomatous inflammation of the distal airways and lung parenchyma. It is related to intense or repeated inhalation of various antigens, including thermophilic bacteria, fungi, bird excreta, and chemical agents. This condition has been described in patients exposed to Aspergillus spores and has been implicated in farmer's lung disease and malt-worker's lung disease.¹⁴² The acute form of the disease presents within hours of exposure to the antigens with dyspnea, cough, fever, and myalgia. The chest radiograph usually shows interstitial and alveolar nodular infiltrates. Repeated exposures to the offending antigens lead to a chronic form of hypersensitivity pneumonitis that is associated with irreversible pulmonary fibrosis.^{142,143} Serum levels of IgG antibodies to Aspergillus are elevated when the disease is due to Aspergillus.¹⁴⁴ The management of the acute form includes avoiding further exposure to the offending agents and corticosteroid therapy.^{142,145}

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