Pulmonary Aspergillosis

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Introduction

The term aspergillosis refers to all diseases produced by the various species of the *Aspergillus* fungus. These diseases are associated primarily with the respiratory system and constitute what is termed pulmonary aspergillosis.

Pulmonary aspergillosis, like other fungal infections, has been on the rise for the last 2 decades,[1-3] probably as a result of greater life expectancy and the increase in immunocompromised patients due to antineoplastic treatment, an increase in the number of transplant recipients, and infections like acquired immunodeficiency syndrome (AIDS).

Pulmonary aspergillosis constitutes one of the most serious infections to be found in hospitals, with a mortality rate between 50% and 85%.[4-6] Although fungal infections have always been associated with patients with marked immunosuppression, in the last 15 years numerous studies have been published linking this infectious complication to critically ill patients. Thus, in the multicenter European EPIIC[7] (European Prevalence of Infection in Intensive Care) study, and in the last multicenter studies of 2 Spanish study groups (EPIFUCI and EPCAN)[8,9] on the epidemiology of fungal colonization and infections in intensive care units (ICU) it was shown that among ICU-acquired infections of known etiology, funguses represent the fourth most commonly isolated microorganism, and *Aspergillus* is one of those most frequently implicated.

It was Michelli who in 1729 first described the genus *Aspergillus*. The fungus is ubiquitous, an example of an "opportunistic pathogen" that typically affects patients with compromised defense mechanisms. To date, approximately 900 species of *Aspergillus* have been identified. Raper and Fennel[10] classified them into 18 groups, only 12 of which are related to human disease. The vast majority of these diseases are caused by 4 species: *A fumigatus* (65%-75%), *A flavus* (5%-10%), *A niger* (1.5%-3%), and *A terreus* (2%-3%).

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Manuscript received June 16, 2003. Accepted for publication June 25, 2003.

As *Aspergillus* is airborne, outbreaks of aspergillosis in institutions such as hospitals can lead to epidemics with considerable clinical repercussions, especially in patients at risk or exposed to large quantities of spores. The main portals of entry for the fungus are the lung and the paranasal sinuses. Epidemics can occur through contamination of ventilation systems due to construction in or near the institution. Spores can remain airborne for prolonged periods and contaminate any surface in contact with the air. Recently it has been suggested that water as well can act as a reservoir for the fungus.[11]

The simultaneous presence and interaction in a given patient of 3 factors will determine whether *Aspergillus* infection will develop: the virulence of the fungus, the type and amount of exposure, and the immunologic status of the patient. In some cases a clear progression from colonization to invasive disease has been described (Figure[12]). Human beings have a remarkable capacity to eliminate *Aspergillus* with the help of the alveolar macrophages, which ingest and destroy inhaled spores. Thus, risk factors for invasive infection by *Aspergillus* may be associated with alterations in macrophage and neutrophil function, which may explain why infection mainly affects bone marrow and solid organ transplant recipients, patients with neutropenia, or those who have received corticosteroid treatment. Other risk groups are patients with AIDS, those with chronic granulomatous disease, drug users, patients with sarcoidosis, severe burn patients, and alcoholics.[13,14] Aspergillosis can also develop when no risk factors are present. Thus, cases have been described of community-acquired pneumonia due to *Aspergillus* in apparently immunocompetent patients,[15] but it is likely that the patients had some undetected defect in macrophage and neutrophil function that permitted invasive infection to develop.

Clinical Presentations of Pulmonary Aspergillosis

Although in some cases *Aspergillus* may be implicated in diseases like extrinsic allergic alveolitis, asthma, and mycotoxicosis, we will limit our discussion here to processes in which *Aspergillus* is the main etiologic agent (Table 1).

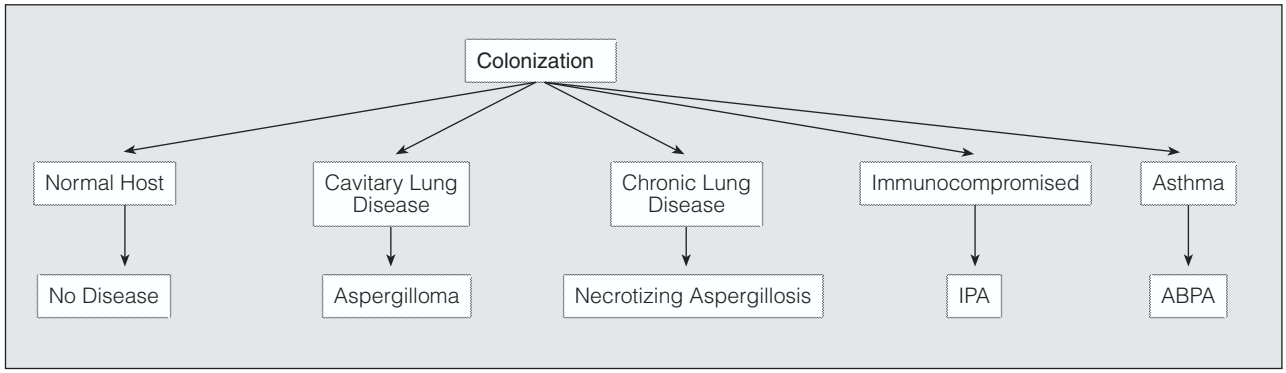

Figure. Clinical results of inhaling *Aspergillus* spores. IPA indicates invasive pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis. (Adapted from Soubani et al.[12])

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a disease produced by the inhalation of *Aspergillus* spores and their subsequent growth on the bronchial mucosa. The disease is not invasive, and is limited to the bronchial tree. Its pathogenic mechanism is based on a hypersensitivity reaction (type I, immunoglobulin [Ig] E-mediated, and type III, IgG-mediated) produced by *A fumigatus* antigens, with the formation of immune complexes that give rise to eosinophilic infiltration damaging the bronchial wall; for the immune complex to cause tissue lesion, the presence of IgE is essential.

ABPA mainly affects patients with persistent asthma or severe, corticosteroid-dependent asthma (with a prevalence of between 1% and 2%[16]), and patients with cystic fibrosis, in whom prevalence is greater[17] (between 2% and 15%).

The clinical manifestations of the disease are low-grade fever, cough, purulent expectoration, and dyspnea, as well as hemoptysis and chest pain. Physical examination reveals prolonged exhalation and rhonchi in most patients, while crepitations are heard on auscultation when pulmonary infiltrates are present.

In laboratory tests, eosinophilia (generally more than 1000 cells/μL) is found in most patients. Sputum eosinophils are also usually present, and total and specific IgE concentrations are elevated (total IgE>800-1000 μg/mL). Determining IgE levels helps to identify those asthma patients who are sensitive to the fungus, but do not have ABPA. Concentrations are the best indicator of disease activity,[18] and should therefore be monitored regularly. On occasion, values may remain high in patients who have responded to corticosteroid treatment. In bronchoalveolar lavage (BAL), concentrations of specific IgE are also increased, which reflects the role of the lung as an immunologically specific organ, although this has no effect on diagnosis or treatment decisions.

Tests for precipitins to *Aspergillus* species (specific IgG) are positive in more than 90% of cases, but negative results do not rule out the diagnosis.

Cutaneous reactivity to *Aspergillus* antigens can be either immediate (IgE-dependent) or delayed (4-8 hours). Only the delayed reaction is inhibited by corticosteroids, and a negative skin test does not rule out a diagnosis of ABPA. Such reactions also occur in patients with asthma, aspergilloma, and other chronic lung diseases.

Chest x-rays commonly show fleeting, patchy infiltrates, characteristically involving the upper lobes. Mucus plugs may cause segmental, lobar, or total atelectasis. Bronchial inflammation and dilatation are reflected in the typical "tram line," "gloved finger," and "ring" signs. High resolution computed tomography is the best radiologic method for showing the presence of bronchiectasis, which is usually central and affects the proximal airway. In advanced stages, loss of volume in the upper lobes or signs of fibrosis with extensive "honeycombing" can be observed.

Based on clinical and radiological findings, Patterson et al[19] have proposed 5 stages of ABPA. These are not necessarily phases of the disease and there is no inexorable progression from one to the other (Table 2).

A diagnosis of ABPA requires radiological and immunological confirmation within an appropriate clinical context. In 1977 Rosenberg et al[20] established the diagnostic criteria that Greenberger and Patterson[21] improved in 1986 by incorporating serum parameters (Table 3).

It must be remembered that all the diagnostic criteria are not always present at the same time in a given patient. To delay treatment until all symptoms develop and bronchiectasis appears is an error that can lead to irreversible pulmonary lesions. ABPA can be subdivided

TABLE 1
Clinical Syndromes of Pulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis
Bronchocentric granulomatosis
Invasive pulmonary aspergillosis
Tracheobronchial aspergillosis
Chronic necrotizing pulmonary aspergillosis
Aspergilloma or mycetoma

TABLE 2
Clinical Stages of Allergic Bronchopulmonary Aspergillosis*

Stage	Sings and Symptoms	Radiography	Serum IgE		Eosinophilia	Precipitins
			Total	IgE-Af		
I (acute)	Cough, dyspnea, fever, expectoration, pain	Fleeting infiltrates	+++	+	+	+
II (remission)	No symptoms	No infiltrates	+	±	–	±
III (exacerbation)	Symptoms	Infiltrates	+++	+	+	+
IV (corticosteroid-dependent asthma)	Persistent dyspnea	No infiltrates	++	±	±	±
V (fibrotic)	Dyspnea, sputum production, cyanosis, clubbing	Fibrosis/honeycombing atelectasis	+	±	–	±

*IgE-Af indicates IgE specific for *Aspergillus fumigatus*; + indicates present or elevated; – indicates normal or absent.

into 2 groups: with and without bronchiectasis.[22] There are 5 diagnostic criteria for patients in the first group (ABPA-central bronchiectasis): asthma, central or proximal bronchiectasis, elevated total serum IgE concentration, immediate skin reactivity to *Aspergillus* species, and elevated specific IgE and/or IgG serum levels, at least compared to concentrations in asthma patients with positive skin tests for *Aspergillus* species and without ABPA. The minimum criteria for diagnosis in patients in the second group (ABPA-seropositive) include asthma, immediate positive reaction in skin test, elevated total serum IgE concentration, pulmonary infiltrates, and elevated specific IgE and IgG titers.

There is a wide difference of opinion among the various cystic fibrosis units as to the number and type of criteria to use in patients with cystic fibrosis and classic ABPA. Table 4 shows those established at the consensus conference of the Cystic Fibrosis Foundation.[23]

The treatment of choice for ABPA is corticosteroids, which have been shown to achieve remission of symptoms and pulmonary infiltrates, lower IgE concentrations, and control peripheral eosinophilia.[24-26] The initial dose of prednisone is 0.5 mg/kg/d for 2 weeks, to be decreased gradually. Duration of treatment depends on the individual patient; however, most will need prolonged treatment to control symptoms and avoid recurrences.[26,27] Inhaled corticosteroids have not proven their efficacy in preventing the disease progression and pulmonary lesions associated with ABPA.[28]

Inhaled natamycin,[29] clotrimazole,[30] and ketoconazole[31] have been tested as antifungal treatments, but their efficacy has not been demonstrated. Recently a randomized, double blind, placebo-controlled trial has been published on the effect on ABPA of treatment with itraconazole at a dose of 200mg per day for 16 weeks. Treatment led to improvements in symptoms, lung function, and exercise tolerance, as well as to a decrease in IgE concentrations and reduced doses of corticosteroids.[32] Despite these results, it is not a first line drug in ABPA therapy, but can be turned to when prednisone treatment is not sufficient.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis is an entity characterized by the presence of necrotizing granulomas that obstruct and destroy bronchi and bronchioles. Granulomatous inflammation may spread to nearby pulmonary arterioles. Its exclusive bronchial localization, with no extrapulmonary lesions, distinguishes it from other vasculitic and granulomatous processes. It has been suggested in recent years that bronchocentric granulomatosis should not be considered

TABLE 3
Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis

Major
- Asthma
- Immediate cutaneous reactivity to *Aspergillus* species (Prick test)
- Total serum IgE >800-1000 ng/mL or >400 U/mL
- Precipitins positive to *Aspergillus* species
- Increased IgE and IgG specific for *Aspergillus* species
- Pulmonary infiltrates
- Proximal bronchiectasis
- Peripheral eosinophilia (>1000 eosinophils/μL)

Minor
- Presence of *Aspergillus* species in sputum
- Brown mucus plugs
- Delayed cutaneous reactivity (4-6 hours)

TABLE 4
Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis in Patients With Cystic Fibrosis*

- Reversible bronchoconstriction and/or clinical and lung function deterioration not due to bacterial exacerbation and that does not improve with antibiotic therapy
- Immediate cutaneous reactivity to *Aspergillus* species (Prick test)
- Elevated total serum IgE (>400 U/mL)
- Elevated specific serum IgE (CAP ≥ class 2)
- The following should also be considered:
  - Peripheral eosinophilia (>400 eosinophils/μL)
  - Precipitins positive to *Aspergillus* species
  - Consistent chest x-ray and computed tomography

*CAP indicates CAP system (Pharmacia, Uppsala, Sweden).

TABLE 5
Risk Factors for Invasive Pulmonary Aspergillosis

1. Prolonged neutropenia (>3 weeks) or neutrophilic dysfunction (chronic granulomatous disease)
2. Transplantation (greater risk in bone marrow and lung transplantation)
3. Hematologic malignancy (especially leukemias)
4. Corticosteroid treatment (especially when prolonged and at high doses)
5. Cytotoxic treatment
6. AIDS

an entity in itself, but merely a pathologic diagnosis.[33]

Patients with bronchocentric granulomatosis are frequently chronic asthmatics with peripheral eosinophilia and elevated IgE serum levels. In more than 50% of cases *Aspergillus* species are found to be present in airway granulomas[34]; in these cases, bronchocentric granulomatosis is interpreted as a bronchial reaction of hypersensitivity to the *Aspergillus* antigen and is closely related to ABPA. Bronchocentric granulomatosis has also been described in nonasthmatic patients with rheumatoid arthritis, Wegener´s granulomatosis, or red cell aplasia.[35] In these cases a similar immunopathogenic mechanism has been suggested, although the origin of the necrotizing granulomatous reaction is unknown.

Prognosis is better in the group of patients with asthma, who respond well to corticosteroid treatment.

Invasive Pulmonary Aspergillosis

Invasive pulmonary aspergillosis (IPA), which is frequently fatal, is the most serious of the diseases caused by *Aspergillus*. According to autopsy data,[3] it is estimated that the incidence of invasive mycoses increased 14-fold in the 12 years prior to 1992 (rising from 0.4% to 3.1% between 1978 and 1992); the incidence of IPA in particular rose from 17% to 60% and affected 4% of patients who died in hospital.

IPA mainly affects immunocompromised patients[12]; risk factors are shown in Table 5. The most important of these factors is neutropenia,[36] and it is estimated that IPA accounts for 7.5% of all infections in neutropenic patients. Bone marrow transplantation is the type of transplantation that presents the greatest risk of all. This was shown in a broad review[37] of 595 patients with IPA, 32% of whom had undergone bone marrow transplantation, 29% of whom had hematologic malignancy, 9% of whom had received a solid organ transplant, and 8% of whom had AIDS. In 2% of patients no risk factor was found. Although infrequent, there have also been cases of IPA in immunocompetent patients[15] or patients with mild immunosuppression associated with alcoholism, chronic liver disease, diabetic ketoacidosis, sarcoidosis, and burns.[13,14] In recent years some cases of IPA in patients using corticosteroids for chronic obstructive pulmonary disease (COPD) have been reported.[38,39] Alterations in the pulmonary parenchyma in these patients probably constitute a favorable anatomic substrate for fungal invasion.

Pathologically, infection is characterized by a proliferation of fungus mycelia in the pulmonary parenchyma, which causes necrotizing pneumonitis with invasion of the pulmonary vessels, leading to hemorrhage and infarction.

IPA can present in various clinical forms[18] that may appear concurrently or independently:

– *Aspergillus pneumonia.* The clinical picture of *Aspergillus* pneumonia is similar to that of bacterial pneumonia. Initially the chest x-ray may show only an infiltrate or pneumonitis progressing to a condensation that can affect one or both lungs. Although the disease is widespread, *Aspergillus* is isolated from sputum in fewer than half of patients.

– *Angioinvasive aspergillosis.* Vascular invasion and dissemination lead to thrombosis and necrosis. Signs and symptoms include pleuritic pain, dyspnea, and hemoptysis. Initial chest x-ray may be normal in a third of patients, with oval or triangular infiltrates with or without pleural effusion appearing later on. Computed tomography shows nodular lesions with a surrounding halo; pathologically, these images represent zones of necrosis surrounded by peripheral hemorrhage.

– *Tracheobronchial aspergillosis infection.* Localized in the airway, with membrane and ulcer formation. the tracheobronchial form is characterized by *Aspergillus* hyphae invading the airway, forming plugs containing mycelia, inflammatory cells, and necrotic material that cause airway obstruction leading to dyspnea. Approximately 10% of patients with IPA develop this form, which may appear in isolation or accompanied by bronchopneumonia. This clinical presentation is most frequent in lung transplant recipients and AIDS patients.[40,41]

The high mortality and poor prognosis of IPA make early diagnosis and treatment essential. Early diagnosis, in practice, is usually empirical in immunocompromised patients, given that invasive methods are needed to obtain tissue samples to demonstrate the presence of the fungus for a firm histologic diagnosis. However, a diagnostician will need a high index of suspicion, which will be based on the level of risk for developing IPA. In a recent study[42] the impact and interpretation of sputum cultures positive for *Aspergillus* species were assessed for different groups: when patients presented a high risk for developing IPA, as is the case of bone marrow transplant recipients or patients with hematologic malignancies, positive sputum culture can be interpreted as infection; in patients with lower risk, such as those with cystic fibrosis or connective tissue disease, these findings can be interpreted as more probably due to colonization; and in intermediate risk groups, such as solid organ transplant recipients or patients treated with corticosteroids, further clinical information is needed to predict development of the disease. A sputum culture

negative for *Aspergillus* species does not rule out the disease and can be found in up to 70% of patients with a confirmed diagnosis of IPA.[42] Blood cultures, with high specificity (around 97%) but low sensitivity (30%-50%), are rarely positive,[43] but are helpful in BAL, especially when there is diffuse pulmonary involvement.[44] Transbronchial biopsy does not increase the diagnostic yield of BAL.

New diagnostic strategies include high resolution computed tomography[45]; detection of circulating *Aspergillus* antigens (galactomannan and β-D-glucan, with a specificity of 97% and 84% respectively, and with 14% false positives)[46,47]; and detection of *Aspergillus* DNA in serum and BAL by means of a polymerase chain reaction, with high specificity and greater sensitivity than the above-mentioned strategies, but with a high rate of false positives.[48-50] The National Institute of Allergy and Infectious Diseases, in the United States of America, has established the following diagnostic classifications.[37] Diagnosis of IPA is definite when histological examination shows *Aspergillus* hyphae (with or without positive culture from the sample), or when culture of a sample obtained by invasive means, such as transbronchial biopsy, fine needle aspiration, or open-lung biopsy is positive. Diagnosis is probable when the clinical picture is consistent with the disease, and when 2 positive sputum cultures or 1 positive BAL, bronchial lavage, or brushing culture shows *Aspergillus* hyphae, or when fungus antigens are detected in serum or BAL. Diagnosis is possible when there is only a clinical picture consistent with the disease.

Treatment should be initiated as soon as there is suspicion of IPA. Success will depend on early diagnosis and absence of dissemination, as well as on initiation of intense antifungal treatment and resolution of the patient´s immunological problems, such as neutropenia, or the suspension of immunosuppressive treatment. The most immunosuppressed patients, such as bone marrow transplant recipients or patients with hematologic malignancy, do not respond to treatment as well as less immunocompromised patients do (28% compared to 51%). Response is also better when the disease is confined to the lung than when infection is disseminated (48% compared to 18%).[37]

Amphotericin B is the drug most widely used in the treatment of IPA.[43] The initial dose is 0.6 to 1.2 mg/kg/d, infused intravenously. When higher doses are needed to treat severe infections, however, adverse effects—mainly kidney damage, electrolyte disturbances, and hypersensitivity reactions—are more common. The response rate varies widely, between 20% and 83%.[43] Lipid amphotericin preparations (amphotericin B liquid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion) have been introduced in an effort to reduce these side effects, as they allow the administration of high doses with less toxicity. However, they have not been shown to be more effective than amphotericin B deoxycholate,[51,52] for which reason they are not recommended as first line drugs, except in patients at high risk of kidney damage or who have already developed it during amphotericin B therapy. The optimum duration of amphotericin B therapy is unknown, but it is recommended that it be maintained until the disease is clinically and radiologically resolved, the cultures (if obtained) negative, and the immunocompromised state resolved or improved.[43]

The oral formulation of itraconazole, another antifungal drug used to treat IPA, has been evaluated in 2 large studies[53,54] with complete or partial response in 39% of patients and failure in 26%. Results were particularly poor in AIDS patients and in allogeneic bone marrow transplant recipients. Itraconazole is now available in a formulation for intravenous infusion, which is better absorbed and has achieved better plasma concentrations and response rates than the oral formulation.[55] It seems reasonable to consider treatment with itraconazole as an alternative to amphotericin B in less immunocompromised patients and in later stages of IPA, after initial control of the disease has been achieved with amphotericin B.[35,43]

Caspofungin is another antifungal drug recently approved by the Food and Drug Administration to treat fungal diseases, among them IPA.[56] It is the first drug of its type (glucan synthesis inhibitor) and its most significant property is that it is active against both *Aspergillus* and *Candida*, with low risk of toxicity. Nevertheless, pending further studies, its use in IPA therapy at the present time is limited to patients with refractory infection or intolerance to conventional treatment.

Voriconazole is a new azole antifungal agent that has been shown in initial studies to be active against *Aspergillus.* Findings from 2 recent studies,[57,58] in which voriconazole and amphotericin B were compared in initial treatment of IPA, showed superior results for voriconazole with regard to response rate and survival, with fewer toxic effects.

Other forms of treatment include surgery for localized lesions in patients with continuous immunosuppression or massive hemoptysis, and immunomodulatory therapy (granulocyte and macrophage colony-stimulating factors, granulocyte transfusion, interferon γ, etc.). Immunomodulatory therapy, which aims to increase phagocytosis and reduce the damage caused by aspergillosis, is still in the experimental stage and has not been shown to increase survival rates.[59-61]

Another important approach to managing IPA is prophylaxis in the population at risk. The strategy includes the use of intravenous or aerosol amphotericin B at low doses, as well as other antifungal drugs, such as fluconazole. Their efficacy in trials, however, has been highly variable.[62-64]

Despite intensive treatment and early diagnosis, mortality from IPA is still extraordinarily high (between 57% and 100%) and is influenced by such factors as the presence of 2 or more risk factors, underlying disease, duration and type of immunosuppression, ICU stays,

development of adult respiratory distress syndrome, mechanical ventilation, multiorgan failure, and early diagnosis and initiation of treatment.[4,65]

Tracheobronchial Aspergillus Infection

Tracheobronchial aspergillus infection is an invasive infection confined to the bronchial tree that can appear either in isolation or as a manifestation of IPA. In isolation, the disease is characterized by bronchial inflammation that is intense, but does not affect the pulmonary parenchyma.

The 2 groups of immunocompromised patients with the highest incidence of tracheobronchial aspergillus infection are solid organ (mainly lung and heart) transplant recipients and AIDS patients.[40,41,66,67] Histologically, infection is characterized by the presence of *Aspergillus* hyphae in the basal membrane of the airway with intense inflammation, edema, ulcers, plaques, or pseudomembranes. Tracheobronchial aspergillus infection can present in 3 distinct forms: *a)* tracheobronchial aspergillosis, with the presence of edematous and inflamed bronchial mucosa; *b)* pseudomembranous tracheobronchial aspergillosis, with the presence of whitish membranes or large plugs occluding the lumen due to the accumulation of hyphae and necrotic material, and *c)* an ulcerative form, which is the most serious and can be recognized by the presence of necrotizing ulcers in the bronchial mucosa. In lung transplant recipients, these lesions are usually located in the bronchial anastomosis.

The signs and symptoms of the 3 forms vary. Initially there are few, but fever, dyspnea, cough, or hemoptysis may appear in the course of disease. Radiologically, the only alteration may be the presence of patchy atelectasis related to the mucus plugs and hyphae.

A presumptive diagnosis is made when the fungus is isolated from bronchial aspirate or BAL cultures, and a definitive diagnosis when there is histologic demonstration of invasion of the mucosa by hyphae.

Treatment includes oral itraconazole and inhaled or systemic amphotericin B; in some treatment regimens a combination of itraconazole and amphotericin B is used.[40,67] Response to treatment is good in approximately 80% of patients.[40,68,69]

Although the outcome with treatment is usually favorable, in some cases of tracheobronchial aspergillosis invasion of blood vessels may occur, giving rise to disseminated forms like IPA. The disease may even spread to organs other than the lung.

Chronic Necrotizing Aspergillosis

Also known as semi-invasive aspergillosis, chronic necrotizing aspergillosis is a destructive process of the lung caused by *Aspergillus* invasion. It differs from IPA in that there is localized invasion of the pulmonary parenchyma, with no vascular invasion and, consequently, no dissemination to other organs.

The process is a chronic one that progresses slowly over months or years.[66] Although rarely found in hospital settings, it has been described in patients in chronic care centers, where it affects patients with altered local pulmonary defense mechanisms and/or mild immunosuppression. Most of these are older patients who have undergone pulmonary resection or radiation, those with tubercular lesions, or those with such underlying diseases as COPD, bronchiectasis, pneumoconiosis, or, rarely, sarcoidosis.[70,71] Mild immunosuppression may be due to alcoholism, diabetes, malnutrition, low doses of corticosteroids, or diseases such as rheumatoid arthritis and ankylosing spondylitis.

Signs and symptoms, such as cough, expectoration, and dyspnea progress slowly and are often confused with those of the underlying disease. Fever, weight loss, and leukocytosis are also frequent. Chest x-rays show infiltrates, mainly in the upper lobes, and as the disease progresses adjacent pleural thickening and cavities containing a fungus ball may appear,[71] all a consequence of the lung tissue necrosis that accompanies the invasive process. This distinguishes chronic necrotizing aspergillosis from aspergilloma, in which the fungus grows inside a pre-existing cavity.

A definitive diagnosis requires histologic demonstration of invasion of lung tissue by *Aspergillus* and positive culture of samples, but transbronchial biopsy and fine-needle aspiration biopsy are rarely positive.[72] Immunocompromised patients, due to the nature of their underlying disease, do not usually undergo open-lung biopsy. Consequently, diagnosis will be based on clinical and radiological findings consistent with the diagnosis in patients at risk who do not respond to conventional treatment; on the isolation of *Aspergillus* species from sputum, bronchial aspirates, or BAL; and on ruling out other conditions with similar presentations, such as active tuberculosis, histoplasmosis, or coccidioidomycosis.[12]

Response to treatment with amphotericin B is generally good and itraconazole as a complementary treatment may be an option.[72] Surgery is limited to younger patients with localized lesions who do not respond to conventional treatment.

Aspergilloma

Aspergillosis is generally considered the most frequent and most easily recognized clinical form of pulmonary aspergillosis, although there are no data to support such an assertion.[42,73] All species of *Aspergillus* can produce aspergilloma, which arises as a result of the colonization of a pre-existing cavity, cyst, or bulla, or as a consequence of chronic diseases such as tuberculosis, bronchiectasias, bullous emphysema, advanced stages of pulmonary fibrosis or sarcoidosis, ankylosing spondylitis, or pulmonary infarction. It has also been described in cavities produced by other fungi. Of these diseases, it is most frequently tuberculosis that predisposes to aspergilloma.[74]

The real incidence of aspergilloma is unknown. In 1970 the British Tuberculosis and Thoracic Association[75] published a study of 544 patients with tuberculous cavities, of whom 11% had radiologic signs of aspergilloma.

An aspergilloma develops as a consequence of inadequate drainage of the lung cavity, where the fungus can then grow, forming a "ball" composed of *Aspergillus* hyphae, fibrin, mucus, and cellular debris. It is generally a noninvasive process with only saprophytic colonization and no invasion of surrounding parenchyma or blood vessels, but on rare occasions there may be local invasion and progression to chronic necrotizing aspergillosis or even to a disseminated form such as IPA.

The interval between the diagnosis of pulmonary tuberculosis and the development of an aspergilloma is very variable (from 1 to 30 years). The aspergilloma can be present for years without producing signs or symptoms. The most frequent of these is hemoptysis, which appears in 70% to 90% of patients; hemoptysis is often mild, but on occasion it can be massive and perhaps life threatening, with a mortality rate between 2% and 14%.[12,18,43] Massive hemoptysis, most frequent when the underlying disease is tuberculosis, is due to the erosion of bronchial arteries, with no relation between the amount of blood and the size of the pulmonary lesion.

Diagnosis is usually made on the basis of radiological findings or during the evaluation of an episode of hemoptysis. Radiologically, the aspergilloma is usually found in the upper lobes, appears as a well-differentiated mobile soft-tissue mass within a cavity, with air between the mass and the cavity wall. There may also be adjacent pleural thickening. The typical image may not show up clearly in a simple chest x-ray, and computed tomography may be needed to visualize it. Movement of the aspergilloma when the patient changes position is a very characteristic but variable sign.[71]

Sputum culture is positive in 50% of cases, precipitins are positive in all patients, and there may be false negatives in rare cases of aspergilloma due to species other than *A fumigatus* or in patients receiving corticosteroid treatment. Skin tests are positive in a minority of patients.[72]

The natural history of aspergilloma is variable. In most cases the lesion remains stable, in 10% it decreases in size and may even disappear spontaneously, and in very rare cases it increases in size. The risk factors associated with a poor prognosis are increase in the number and size of lesions, immunosuppression, massive and recurrent hemoptysis, and sarcoidosis or AIDS as underlying diseases.[43]

There is no consistent evidence that aspergilloma responds to antifungal treatment, as these drugs rarely reach minimal inhibitory concentration in lung cavities. Trials with antifungal agents administered via inhalation and intracavitary or endobronchial instillation have not met with much success.[76-78] With some of these drugs hemoptysis was observed to cease, but without radiological resolution and with a high recurrence rate. Intravenous amphotericin B has not been proven effective against aspergilloma, and well-designed trials are still needed to show the usefulness of itraconazole.[72,73]

Bronchial artery embolization is another treatment modality that may be considered for patients with hemoptysis failing to respond to antifungal therapy and in whom surgery is contraindicated. The technique is often less than satisfactory because of the difficulty of locating the bleeding vessel and the development of collateral circulation. If the curative measure is effective, it is only temporarily so and the rate of recurrence is high.[12,18,43]

Surgery offers clear benefits, such as control of hemoptysis, improvement in quality of life, and increased survival.[74] However, it is a high-risk technique, particularly in patients with advanced chronic disease, pleural thickening, and sometimes in those with mediastinal fibrosis. Mortality is higher than 25%, and the rate of complications, especially bleeding, bronchopleural fistulas, and empyema, is high.[74] In recent studies mortality was reported to be lower,[75-80] but most of the patients in question were young, had good lung function, and almost all had tuberculosis as the underlying disease.

In summary, observation together with conservative measures is the most appropriate approach in cases of aspergilloma with no major complications. Surgery should be considered in patients with massive hemoptysis and good respiratory reserve.

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