Aspergillosis

Abstract

Aspergillosis is a large spectrum of fungal diseases, which primarily affect the lungs and are caused by members of the genus Aspergillus. A. fumigatus seems to be the most frequent species. The transmission of fungal spores to the human host is via inhalation. The clinical manifestations depend upon the immunological state of the patient, and range from hypersensitivity reactions (allergic bronchopulmonary aspergillosis (ABPA)) to noninvasive colonization of previously damaged tissue (pulmonary aspergilloma) to acute or chronic limited invasive disease (chronic necrotizing pulmonary aspergillosis (CNPA)) to rapidly progressive invasive disease (invasive aspergillosis (IA)). ABPA occurs in conjunction with asthma and cystic fibrosis. CNPA is a sub-acute process most commonly associated with underlying lung disease, alcoholism, or chronic corticosteroid therapy. Aspergilloma is a fungus ball that develops in previous cavitary lung lesions. IA is an often-fatal infection that occurs in severely immunosuppressed patients, and is characterized by invasion of blood vessels. Dissemination to other organs may occur. The incidence of IA was reported to vary between 3 and 7% in bone marrow transplant (BMT) patients, 1.5 to 4% in liver transplant recipients, approximately 10% in lung transplant recipients, and 14% in patients with onco-hematological diseases and cardiac transplant recipients. Diagnosis is based on histopathological findings and immunodetection of specific antigens. Prophylaxis consists in isolating high-risk patients in laminar air flow (LAF) rooms. Voriconazole, itraconazole, the investigational azoles (posaconazole, ravuconazole, anidulafungin and micafungin) with anti-mould activity, and amphotericin B all possess a reasonably broad spectrum of activity against Aspergillus. Despite advances in therapy, the invasive forms of aspergillosis are often associated with significant morbidity and mortality.

Key-words

Aspergillosis, Allergic bronchopulmonary aspergillosis (ABPA), Chronic necrotizing pulmonary aspergillosis (CNPA), pulmonary aspergilloma, invasive aspergillosis (IA), azoles
Definition
Aspergillosis is a large spectrum of fungal diseases, which primarily affect the lungs and are caused by members of the genus Aspergillus. Aspergillus species are ubiquitous molds in the environment and are especially common in the soil and decaying vegetation. The genus Aspergillus includes over 185 species. Around 20 species have been reported as causative agents of opportunistic infections in human beings. Among these, A. fumigatus is the most commonly isolated species, followed by A. flavus and A. niger, A. clavatus, A. glaucus, A. nidulans, A. oryzae, A. terreus, A. ustus, and less commonly A. versicolor. The transmission of fungal spores to the human host is via inhalation.

Clinical presentation of the diseases
Aspergillus can affect different organ systems. The most frequently involved organs are the lungs. The clinical manifestations of lung aspergillosis are the following: allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing pulmonary aspergillosis (CNPA), aspergilloma, and invasive aspergillosis (IA). The clinical manifestations and severity of Aspergillosis depend upon the immunological state of the patient (Cohen, 1991). In patients who are severely immunocompromised, Aspergillus may be hematogenously disseminated beyond the lung, potentially causing endophthalmitis, endocarditis, rhinosinusitis, fungemia, osteomyelitis and abscesses in the myocardium, kidney, liver, spleen and soft tissue (Table 1).

ABPA is a hypersensitivity reaction to A. fumigatus colonization of the tracheobronchial tree and occurs in conjunction with asthma and cystic fibrosis (Hinson et al., 1952; Rosenberg et al., 1977).

Chronic necrotizing pulmonary aspergillosis (CNPA) is a sub-acute process usually found in patients with some degree of immunosuppression, most commonly associated with underlying lung disease, alcoholism, or chronic corticosteroid therapy (Binder et al., 1982; Gefter et al., 1981). Because it is uncommon, CNPA often remains unrecognized for weeks or months and causes a progressive cavitary pulmonary infiltrate.

IA is a rapidly progressing, often fatal infection that occurs in patients who are severely immunosuppressed, including those who are profoundly neutropenic, those who have received bone marrow transplant (BMT) or solid organ transplants, and patients with advanced AIDS or chronic granulomatous disease (Ascioglu et al., 2002). This infectious process is characterized by invasion of blood vessels, resulting in multifocal infiltrates, which are often wedge-shaped, pleural-based, and cavitary. Dissemination to other organs, particularly the central nervous system, may occur.

Aspergilloma is a fungus ball that typically develops in the context of preexisting cavitary diseases (Fraser et al., 1998; Kaufman, 1996). Aspergillomas may develop in patients with invasive aspergillosis or chronic necrotizing pulmonary aspergillosis. Underlying causes of the cavitary disease may include treated tuberculosis or other necrotizing infections, sarcoidosis, cystic fibrosis, and emphysematous bullae. The ball of fungus may move within the cavity but does not invade the cavity wall; however, it may cause hemoptysis.

Table 1: Clinical presentation of aspergillosis infections

<table>
<thead>
<tr>
<th>Invasive aspergillosis</th>
<th>Pulmonary aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS aspergillosis</td>
<td>CNS aspergillosis</td>
</tr>
<tr>
<td>Sinonasal aspergillosis</td>
<td>Sinonasal aspergillosis</td>
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<tr>
<td>Osteomyelitis</td>
<td>Osteomyelitis</td>
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<tr>
<td>Endophthalmitis</td>
<td>Endophthalmitis</td>
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<tr>
<td>Endocarditis</td>
<td>Endocarditis</td>
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<tr>
<td>Renal abscesses</td>
<td>Renal abscesses</td>
</tr>
<tr>
<td>Cutaneous aspergillosis</td>
<td>Cutaneous aspergillosis</td>
</tr>
<tr>
<td>Pulmonary aspergilloma</td>
<td>Pre-existing lung cavity</td>
</tr>
<tr>
<td>Colonization</td>
<td>Sinuses, lungs</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Sinuses, lungs</td>
</tr>
<tr>
<td>Others</td>
<td>Cutaneous aspergillosis</td>
</tr>
<tr>
<td></td>
<td>Burns</td>
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<tr>
<td></td>
<td>Post surgical wounds</td>
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<tr>
<td></td>
<td>I.V. insertion sites</td>
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<tr>
<td></td>
<td>Otomycosis</td>
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<tr>
<td></td>
<td>Exogenous endophthalmitis</td>
</tr>
<tr>
<td></td>
<td>Allergic fungal sinusitis</td>
</tr>
<tr>
<td></td>
<td>Urinary tract fungus balls</td>
</tr>
</tbody>
</table>

Risk factors for Aspergillosis infections
Risk factors involved in the development of AI are hematological malignancies (Aisner et al., 1979; Cowie et al., 1994), exposure to steroids, agranulocytosis (intensity + duration), CMV disease, underlying pulmonary disease (Cowie et al., 1994) (including COPD, interstitial lung disease, and previous thoracic surgery) and altered immune status due to chronic corticosteroid therapy (Bodey et al., 1992; Denning et al., 1994; Denning and Stevens, 1990), alcoholism, collagen vascular disease, or chronic granulomatous disease (Beyer et al., 1994) and preexisting cavitary disease.

Patients who have undergone BMT or solid organ transplant, profoundly neutropenic after receiving chemotherapy for hematological malignancies or...
lymphoma, patients with chronic granulomatous disease, and patients with late-stage HIV are also at risk. Specific risk factors for invasive aspergillosis after BMT include prolonged neutropenia, graft versus host disease, high-dose corticosteroid therapy, disruption of normal mucosal barriers, mismatched or unrelated donor transplants, and the presence of central venous catheters. The risk of IA is also related to the degree of exposure to Aspergillus spores (Gefter et al., 1985; Gustafson et al., 1983; Hofflin et al., 1987; Iwen et al., 1993; Janssen et al., 1996).

**Diagnosis**

AI is often difficult to diagnose especially in the early stage. However, early diagnosis is of remarkable significance for earlier initiation of antifungal therapy and reduction of mortality rates. Suspicions of AI should be based on patients with risk factors for infection. Definitive diagnosis requires both histopathologic evidence of acute-angle branching, septated nonpigmented hyphae approximately 3.0 mm in diameter, and culture(s) yielding Aspergillus species from specimens obtained by biopsy from the involved organs (or aspiration from a solid organ) (see Figure 2). Blood, CSF, and bone marrow specimens rarely yield Aspergillus species. The septated hyphae of Aspergillus are best detected by Gomori methenamine silver and periodic acid-Schiff stains, and it would be desirable to include these stains in the initial tissue evaluation if invasive fungal disease is suspected.

Radiographic studies may include characteristic findings such as wedge-shaped pleural-based densities or cavities on plain radiographs (both late findings). Findings on CT scans include the "halo sign" (an area of low attenuation surrounding a nodular lung lesion) initially (caused by edema or bleeding surrounding an ischemic area) and, later, the "crescent sign" (an air crescent near the periphery of a lung nodule, caused by contraction of infarcted tissue). Bronchoalveolar lavage, with assay of the fluid by smear, culture, and/or antigen detection, has excellent specificity and reasonably good positive predictive value for invasive aspergillosis in immunocompromised patients. Transbronchial biopsy or brushings are too often false negative (CIII). Biopsies of endobronchial lesions have been useful when such lesions are encountered (Stevens et al., 2000a).

**Figure 2 (Photos courtesy Pfizer)**

a) Characteristic dichotomous branching of *Aspergillus* sp (45º)
b) Conidial head *Aspergillus fumigatus*

**Immunodetection**

The availability of the Platelia Aspergillus, a sandwich ELISA kit that detects circulating galactomannan, an exoantigen of Aspergillus, has been a major advance for managing patients at risk for invasive aspergillosis because of the early detection of the antigen. The assay is now widely used throughout the world, including the USA. Although initial studies that assessed the performance characteristics of this assay reported high sensitivity and specificity, more recent studies show significant variation in performance. Some of the factors that might affect the release of the Aspergillus antigen bearing the epitope that reacts with the monoclonal antibody EB-A2 used in the ELISA include those relating to fungal growth and leakage of the antigens from the site of infection into the blood, and their binding to substances present in the blood (Mennink-Kersten et al., 2004). Antigen may be detected in other fluids including bronchoalveolar lavage fluid and cerebrospinal fluid (Salonen et al., 2000; Verweij et al., 1999; Viscoli et al., 2002).

**Epidemiology**

In the last decades, the incidence of fungal infections has been increasing. Invasive aspergillosis (IA) is the second most frequent fungal infection in cancer patients, after candidiasis (Anaissie, 1992). The incidence of IA was reported to vary between 3 and 7% in BMT.

Aspergillosis is often associated with significant morbidity and mortality (Denning and Stevens, 1990). Voriconazole, itraconazole, the investigational azoles (posaconazole, ravuconazole, anidulafungin and micafungin) with anti-mould activity, and amphotericin B all possess a reasonably broad spectrum of activity against Aspergillus and the related hyaline moulds. Voriconazole is a new triazole structurally related to fluconazole, but with improved potency and spectrum of activity, including fluconazole-resistant strains of Candida, and most emerging fungal pathogens such as Blastomycetes, Fusarium spp. and Penicillium spp. (Arikan et al., 1999; Clancy and Nguyen, 1998; Chrysanthou and Cuenca-Estrella, 2002; Espinel-Ingroff, 1998; Sanati et al., 1997; Pfaller et al., 2002; 2003). Parenteral administration can be followed by oral therapy. Voriconazole is currently approved in many countries for primary treatment of acute invasive aspergillosis (Herbrecht et al., 2001, Denning et al., 2002, Herbrecht et al., 2002), and salvage therapy for rare but serious fungal infections. The recommended dosage is as follows:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of patients</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>559</td>
<td>65%</td>
</tr>
<tr>
<td>Lipid formulations of Amphotericin B</td>
<td>235</td>
<td>51%</td>
</tr>
<tr>
<td>Itraconazole po</td>
<td>156</td>
<td>34%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>156</td>
<td>24%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>144</td>
<td>29%</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>133</td>
<td>42%</td>
</tr>
</tbody>
</table>

In this table are included only the first line treatment drugs. Other drugs, such as caspofungin, are recommended as second line choice.

Treatment
The treatment and prognosis of AI depends upon the type and severity of the disease as well as the immunological status of the patient. Treatment for chronic necrotizing aspergillosis differs significantly from the treatment of ABPA and aspergilloma (Stevens et al., 2000a). Allergic aspergillosis has been successfully treated with corticosteroids, and itraconazole (Stevens et al., 2000b).

Antifungal therapy and the use of LAF or high-efficiency particulate air (HEPA) filtration of the rooms of the patients who receive BMT and other high-risk patients may prevent invasive aspergillosis.

Invasive aspergillosis may be treated with voriconazole (Herbrecht et al., 2001), amphotericin B (deoxycholate and lipid preparations), and itraconazole (Stevens et al., 2000a; Denning and Stevens, 1990). However, despite advances in therapy, the invasive forms of aspergillosis are often associated with surgical resection is indicated for localized
diseases which failed to respond to prolonged antifungal treatment. Aspergillomas may be treated by surgical resection (Denning and Stevens, 1990; Kauffman, 1996). However, this approach may cause significant morbidity and mortality, therefore it should be reserved for patients at high risk to develop severe hemoptysis (Glimp and Bayer, 1983, Massard et al., 1992).

References


Gefter WB, Albeida SM, Talbot GH, Gerson SL, Cassileth PA, Miller W. Invasive pulmonary aspergillosis and acute leukemia. Limitations in
following bone marrow transplantation. Medicine (Baltimore) 1993; 72:78-89.
Oral DP, Myerowitz RL, Du bois PJ. Patho-