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REVIEW ARTICLE

Pulmonary aspergillosis: clinical presentation, diagnosis and therapy

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Abstract: Pulmonary aspergillosis is a serious threat to those immunocompromised as a result of disease or therapy, and has been identified as a major cause of morbidity and mortality in asthmatic and cystic fibrosis patients. Pulmonary aspergillosis can occur in three principal forms: saprophytic, allergic and invasive. Saprophytic aspergillosis involves colonisation of the airways, without invasion or damage of viable tissue, and may present as an aspergilloma (fungus ball) consisting of a tangled mass of mycelium, fibrin, inflammatory cells and epithelial-cell debris. Necrotic tissue also may be invaded but usually only in those severely immunocompromised. Allergic aspergillosis is referred to frequently as allergic bronchopulmonary aspergillosis (ABPA), and may occur in approximately 25% of asthmatic and 10% of cystic fibrosis patients. ABPA presents as a non-infectious, potentially fatal inflammatory disease where antigens released by the fungal mycelium provoke an immune response. Invasive aspergillosis is probably the most serious form of the disease and involves the invasion of viable tissue. It occurs predominantly in patients with pre-existing lung damage, and can spread to other organs and distant sites in the body. Aspergillomas may be detected on chest X-ray as spherical-shaped objects, whilst allergic aspergillosis may be visualised by radiological techniques and computed tomography (CT) scan. Surgery may be employed in the case of aspergilloma, and chemotherapy relies upon the use of amphotericin B (liposomal and aerosolised) and itraconazole.

Key words: Aspergillosis. Aspergillus. Asthma. Cystic fibrosis. Lung diseases.

Introduction

Aspergillus fumigatus is a saprophytic fungus widely distributed in nature and frequently encountered growing on decaying vegetation and damp surfaces. *A. fumigatus* can present as an opportunistic human pathogen and is the most common aetiological agent of pulmonary aspergillosis, being responsible for 80–90% of cases. Despite the fact that the average person inhales 15–30 *A. fumigatus* conidia per day — and usually more in the autumn and winter — clinically relevant disease is rare unless there is pre-existing lung damage or an impaired immune system. Other members of the genus implicated in disease include *A. flavus*,[1] *A. niger*, *A. nidulans* and *A. terreus*.[2] The incidence of aspergillosis is second only to infection with *Candida* spp., but aspergillosis results in greater mortality, which is as high as 85–95% in cases of invasive aspergillosis.[3]

The actual mechanisms by which *A. fumigatus* colonises the respiratory tract are largely unknown. However, it is believed that immunosuppression in cancer patients and impaired mucociliary clearance in cystic fibrosis and bronchiectasis patients facilitate the growth of the fungus in the lung. The virulence of *A. fumigatus* results from the ability of the fungus to use specific properties to avoid the cellular and humoral defences of the host,[4] correlated with the production of extracellular enzymes and toxins.[2,5,6]

The clinical presentations of aspergillosis can be divided into three main groups: saprophytic, allergic

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and invasive; the latter being the most serious form of disease. It should be emphasised that this classification may be arbitrary and there can be considerable overlap between the different classes of disease. In this review, the features of each type of disease, the factors that contribute to the appearance of each, and the treatment options are considered.

Factors predisposing to aspergillosis

The most common predisposing factor for saprophytic aspergillosis (aspergilloma) is chronic cavitary tuberculosis (TB), and 25% of such patients have a history of this disease.[7] In the cavity, normal clearance mechanisms are impaired or absent, and this may permit adherence and germination of fungal conidia, leading to the development of an aspergilloma. Fraser speculated that the saprophytic form is capable of creating its own cavity, as the hyphae advance, by the secretion of toxins, enzymes, or inflammatory mediators derived from the intercavity inflammatory reaction;[7] however, approximately 80% of aspergillomas develop following treatment for cavitary TB.[8]

In patients with allergic aspergillosis, the main predisposing factors are corticosteroid-dependent asthma[9] and cystic fibrosis[10] (where there is proximal and distal bronchiectasis). Moreover, certain occupations and hobbies may predispose to allergic aspergillosis.[11]

In recent decades, invasive aspergillosis (IA) has emerged as an important disease, owing to the aggressive use of immunosuppressive therapy in the treatment of cancer and leukaemia, causing prolonged neutropenia.[12–15] A recent survey of invasive aspergillosis in 595 patients revealed that 32% were bone-marrow transplant recipients and 29% had haematological malignancy.[16] Solid-organ transplantation, acquired immune deficiency syndrome (AIDS) and pre-existing pulmonary disease were recognised as important predisposing conditions in approximately 25% of cases.[16]

One study[17] showed that 30% of all fungal infections in cancer patients were due to *Aspergillus* spp. During the period 1978–1992, systemic mycoses diagnosed at autopsy rose from 1.5% to 6%, and aspergillosis as the cause of death rose from 17% to 60%.[3] The main risk factor for developing aspergillosis is the level (or lack) of immunocompetence,[7,15] and the most common predisposing disease is neoplasia — particularly acute or chronic myeloid leukaemia in patients who are neutropenic.[13]

Myelosuppression (precursor-cell suppression in bone marrow) is the greatest risk factor for IA, and those patients with acute leukaemia have a 20-fold greater risk of IA than do organ transplant recipients or patients with lymphoma.[18] IA has a particularly poor prognosis in leukaemia patients undergoing chemotherapy (50–60% mortality), where induced neutropenia results. Leukaemia patients receiving chemotherapy become granulocytopenic, and these are the main host immunological defence mechanisms against invasion.[19]

Another group of patients at risk of developing aspergillosis is those undergoing organ transplantation. Such patients receive immunosuppressive treatment to prevent organ rejection, and may be given concomitant corticosteroid therapy.[20] Bone-marrow transplant patients are recognised as being highly susceptible to IA, with mortality rates as high as 90% in some centres.[14] In patients undergoing heart and lung transplantation, incidence of IA is reported as 15–35%, causing the highest levels of morbidity and mortality (40–70%). In some cases, however, infection can be attributed to the direct contact of the organ with the environment during transplantation.[14,21,22]

In addition, antimicrobial agents have been shown to predispose the host to aspergillosis,[17,23] and it has been noted that up to a third of patients with chronic granulomatous disease develop serious or lethal aspergillosis due to a deficiency in their host defence mechanisms.[19]

Saprophytic aspergillosis

Saprophytic bronchopulmonary aspergillosis or 'saprophytic colonisation' is defined as the colonisation of the airways by *Aspergillus* spp., without any evidence of tissue invasion or damage. It occurs mainly in cystic fibrosis patients who have obstructive pulmonary disease and are receiving broad-spectrum antibiotics.[24] Also, it is a common disease of chronic asthmatics, who receive large doses of corticosteroids, and in the cavities of TB patients. *A. fumigatus* conidia are believed to attach to the pulmonary bronchoalveolar epithelial cells, thus avoiding mucociliary clearance by the tracheobronchial mucociliary escalator. Once germinated, the conidia produce dichotomously branched mycelia and sporulating conidiophores (seen only in pulmonary aspergilloma).[24] The clinical presentation of saprophytic aspergillosis is colonisation of the tracheobronchial tree, with or without macroscopic fungus-ball formation, and, in some cases, invasion of necrotic tissue.[7] The three most common forms of saprophytic aspergillosis are as follows:

- *Airway colonisation:* The most common predisposing diseases are asthma, cystic fibrosis and chronic bronchiectasis. Colonies of *Aspergillus* spp. can survive within the thick mucous secretions of the airways and in alveolar spaces, without causing damage to pulmonary tissue.[7]

- *Aspergilloma:* This term is used to describe a 'fungus ball' or mycetomal lesion formed by a tangled mass of mycelia of *Aspergillus* spp. *A. fumigatus* is the usual aetiological agent in aspergilloma,[25] and can colonise any intrathoracic cavity (i.e. parenchymal, bronchial or pleural tissue). The fungus ball consists of both living and dead fungal elements, fibrin and inflammatory cells, epithelial-cell debris and mucus.[26] The ball can be tan in colour, relatively solid and fragmented only with force;[7] the largest documented being 13.5 x 6.0 x 4.7 cm.[18] In contrast to allergic and invasive aspergillosis, in saprophytic aspergillosis the fungus can remain quiescent and may grow for months, or even years, without invading pulmonary tissue.[24] Clinically, the symptoms of aspergilloma resemble tuberculosis and sarcoid disease, and X-ray techniques are used to distinguish between the two.[24] In rare cases, aspergilloma can lead to an invasive form of aspergillosis, but this is believed to be related to the level of immunosuppression.[7,24]
- *Invasion of necrotic tissue:* This is the least common form of saprophytic aspergillosis. It involves the invasion and colonisation of necrotic tissues, infarcted lung and, occasionally, malignant tumours, and differs from aspergilloma, where the tissue that lines the cavity wall is viable and the host defence mechanism is able to prevent deep-seated invasion. This can lead to complications in the classification of the disease, between saprophytic colonisation and true invasive aspergillosis. Fraser[7]suggests that the level of granulocytopenia should be taken into consideration to assess the level of immunocompetence, thus determining if true invasive aspergillosis predominates.

Clinical symptoms of aspergilloma

Symptoms include chronic cough, wheezing, malaise, green/brown sputum and weight loss.[8,27] However, the most common symptom of disease is recurrent haemoptysis, which occurs in 50–80% of patients with aspergilloma.[7,8,24]

Lung epithelial damage correlates with the formation of vascular granulation tissue, which may bleed due to friction of the fungus ball against the epithelial lining of the cavity, the secretion of trypsin-like proteolytic enzymes, toxins from viable or degenerate fungal hyphae, and type III (antigen–antibody) inflammatory reactions resulting in injury to the cavity wall and in haemorrhage.[7,24,26]

Severe haemorrhage (>500 mL/24 hr) occurs in around 5–10% of patients, and surgical excision is the main therapeutic option; however, it is not always successful and should be reserved for cases of severe haemoptysis.[24,28]

Diagnosis of aspergilloma

Diagnosis requires a number of factors to be present as acceptable evidence of disease. Commonly, aspergilloma is identified by chest X-ray as a spherical-shaped object separated from the cavity wall by an air space that shows up as a crescent-shaped translucence. This object is often mobile within the cavity, and can be moved by adjusting the position of the patient.[8] In some cases, the 'ball' can be attached to the cavity lining by granulation tissue.[26]

Sputum cultures or bronchial washings are used in suspected cases, and the fungus grows successfully in 50–60% of cases. However, due to the ubiquitous nature of the fungus,[26] caution should be exercised in interpreting results.

Serological studies, using double diffusions or immunoelectrophoresis on agar gels, have demonstrated the presence of precipitating antibodies in 90–100% of patients, and this provides the basis for a possible screening technique.[24,28] Serum precipitins are found also in cases of bronchial asthma, eosinophilia and infiltrates.

Other diagnostic procedures for aspergilloma include computed tomography (CT) scans of the chest, and bronchography.[26]

Treatment of aspergilloma

This is usually conservative unless massive haemoptysis occurs, which may necessitate surgical resection of the source.[29] One main concern about actively treating the disease is the severe underlying pulmonary condition of the patient, and this will influence the choice of therapy, the therapeutic response and the prognosis.

There is a 7–8% mortality rate in cases where surgery has been performed, and 25% have post-surgery complications.[26] Such complications include extension of the aspergilloma into the chest wall, the development of bronchial arteries, and pleural thickening.[8]

Another treatment option is direct instillation of fungistatic or fungicidal agents into cavities.[28] Despite the wide variety of antifungal agents available for treating the disease, no consistent results have been recorded. This could be attributable to two factors: firstly, drugs such as intravenous (IV) amphotericin B are unable to penetrate the fungus ball within the cavity; and secondly, the 'successful' treatment of the disease may be confused with spontaneous regression, which occurs in 7–10% of cases.[7]

Penetration of the fungus ball also has been achieved by direct instillation of drugs (in liquid form), either alone or in combinations, into the cavity by transthoracic techniques. However, many adverse reactions and poor patient tolerance are encountered using this procedure.[26] Aerosolised amphotericin B has been used to treat pulmonary aspergilloma, without clinical evidence of acute toxicity.[30]

A detailed discussion of the treatment options for aspergilloma is presented by Stevens *et al.*[31]

Allergic aspergillosis

Commonly referred to as allergic bronchopulmonary aspergillosis (ABPA), allergic aspergillosis is a hypersensitivity reaction to the conidia of *Aspergillus* spp. It is a potentially fatal, non-infectious, inflammatory respiratory disease, and *A. fumigatus* is the main aetiological agent seen in up to 80% of cases.[32,33] The main predisposing conditions are asthma and cystic fibrosis, and it is estimated that approximately 25% of asthmatic patients and 10% of cystic fibrosis patients have the condition.[7,28,34,35]

The usual point of entry is the lungs, where the fungal conidia land on the bronchial epithelial surface,[36] become trapped in the viscous secretions of asthmatic[37] and cystic fibrosis patients, and germinate readily at body temperature, forming mycelia that colonise the bronchial tree.[28] *Aspergillus* spp. cause clinical and pathological features due to the germination and growth of conidia, and the constant release of antigens from the proliferating hyphae.[38]

Although the understanding of ABPA has increased recently, significant gaps remain in our knowledge of the exact pathogenic mechanisms involved.[33] It is commonly agreed that recurrent episodes of ABPA cause further damage to bronchopulmonary structures, leading ultimately to end-stage fibrosis and bronchiectasis (chronic dilation of the bronchi and secondary infection, usually of the lower lobes).

Usually, the fungus does not invade the lung parenchyma in a patient with ABPA;[9] therefore, dissemination to other organs is rare.[39] The clinical presentations of allergic aspergillosis are divided mainly into two groups: ABPA, the most common form; and extrinsic allergic alveolitis (EAA), also known as 'farmer's lung' or hypersensitivity pneumonitis.[7]

Allergic bronchopulmonary aspergillosis

First described by Hinson and colleagues in 1952,[11] this paper reported the first three patients with ABPA, two of whom had severe asthmatic attacks and one had recurrent wheezing. All were described as having recurrent episodes of wheezy bronchitis, peripheral blood eosinophilia, fever, sputum production, infiltrates on X-ray, and bronchial plugging by secretions containing *A. fumigatus* hyphae.[9] Subsequently, many reports of ABPA have appeared in the literature.[7]

Extrinsic allergic alveolitis

This is a form of hypersensitivity disease that occurs in non-allergic, non-atopic individuals after heavy inhalation of *A. fumigatus*[24] or *A. umbrosus*[40] conidia. It has been recorded in distillers and brewers working with barley, and those who work with mouldy oats or straw on farms.[24] Owing to their small size (2.5–4.5 μm), *A. fumigatus* conidia are deposited at the peripheral pulmonary tissue, resulting in EAA in susceptible individuals. The conidia produce an acute cellular inflammatory response (mainly lymphocytes and plasma cells[24]) within the alveoli, and lesions composed of microgranulomatous tissue develop, which resolve when exposure to the *A. fumigatus* conidia ceases.

Symptoms begin four to six hours after exposure and last up to 18 hours, with the patient experiencing chills, fever, headache, cough and malaise.[24,28] Prolonged exposure can lead to 'honey-combing' seen on chest X-ray, and, possibly, pulmonary fibrosis. The main diagnostic features of EAA is the presence of immunoglobulin (Ig) G precipitating antibody —which is capable of activating complement — and low serum IgE levels.[41] IgG is present in 90% of patients with EAA,[24] and binds to the conidial surface and, to a lesser extent, the hyphae and phailides of *A. umbrosus*.[40]

EAA patients differ from those with asthma in that they show features of dyspnoea, with influenza-like symptoms of fever and fatigue. Another contrasting feature is the influx of neutrophils into the lungs during the acute phase, and influx of T cells and macrophages during the chronic stage.[41] As with other forms of aspergillosis, the best preventive measure is avoidance of the conidia, but adrenal corticosteroids are capable of relieving symptoms and reducing the possibility of fibrotic development.[24]

Clinical presentation of allergic bronchopulmonary aspergillosis

Onset can occur during childhood and may not be diagnosed for many years, resulting in progressive lung damage and the possibility of death or irreversible obstructive lung function as early as the second or third decade of life.[38]

In most patients, diagnosis is established between the third and fifth decade of life; however, over half the patients have asthma before the age of ten and some develop ABPA by the age of 20.[18] Whether the onset is in childhood or in adult life, clinical presentation is classified into five stages: acute, remission, exacerbation, corticosteroid-dependent asthma, and fibrotic.[9,10]

Sensitisation occurs in patients with ABPA, and causes a variety of immune reactions that lead to the formation of bronchocentric granulomatosis and mononuclear infiltration.[28] The most prominent histological feature is necrotising granulomatous inflammation centred around small bronchi and bronchioles,[42] with the focus sometimes present next to the pulmonary artery.[7]

Fungal hyphae usually can be found in necrotic material within the airway lumen but normally are fewer in number and more degenerative than those found in the mucous plugs.

Diagnosis of allergic bronchopulmonary aspergillosis

A number of problems may be encountered in the diagnosis of ABPA. Peripheral blood eosinophilia can be seen in a number of other diseases, including tuberculosis and sarcoidosis, and allergic bronchopulmonary disease can result from exposure to other causative organisms (i.e. *Candida albicans* and *Pseudomonas aeruginosa*).[9]

Another major problem is that not all the clinical manifestations occur simultaneously; therefore, the diagnosis features of ABPA must be considered as a group, rather than individually.[10] The diagnostic criteria have been elaborated since the original description of ABPA; however, much diagnostic disagreement remains. ABPA may be considered likely when six or seven of the major criteria are present, and definite when all criteria are present (Table 1).

Diagnostic techniques used in the identification of ABPA include X-ray techniques and CT scans,[7,40] and characteristic cutaneous wheal and flare reactivity to *A. fumigatus/Aspergillus* spp. mixtures, based on the skin prick test.[9,10,33,38,43,44] A recent study[45] demonstrated the value of the skin prick test as a screening tool in detecting ABPA in asthmatic patients; whereby ABPA was detected by CT scanning in 25–40% of skin-prick-positive patients.

Total serum IgE levels is another good diagnostic feature of ABPA, and, irrespective of the stage of disease, levels of this immunoglobulin are increased markedly. Levels of IgE decrease by 35% after six weeks of prednisone treatment and increase by 100% in cases that show new X-ray-detectable infiltrates. The levels of IgG precipitating antibody are not as specific as that of IgE, with levels at 3% in normal individuals, 12% in those with asthma, and 32% in ABPA patients.[38]

Treatment of allergic bronchopulmonary aspergillosis

Owing to the ubiquitous nature of the fungus, complete eradication of the conidia from the bronchial tree is an unrealistic goal.[38] Antifungal drugs such as amphotericin B and mycostatin have achieved only poor results,[9] and imidazole, ketoconazole and itraconazole have resulted in only varying success rates.

Table 1. Diagnosis of ABPA, based on clinical, serological and radiological findings

Major criteria	Minor criteria
Asthma (mild to severe)	Tenacious sputum containing aspergillus, interfering with bronchoscopic examination.
Peripheral blood eosinophilia (>1000/mm^3)	History of expectoration of dirty green to brown 'plugs', occasionally blood-tinged, containing *Aspergillus* spp. and eosinophils
History of X-ray-detected pulmonary infiltrates	Arthus reactivity to aspergillus antigens
Elevated total serum IgE levels	
Positive immediate skin test	
Precipitating antibodies to *A. fumigatus*	
Proximal/central bronchiectasis	
Elevated levels of serum IgE and IgG antibodies to *A. fumigatus*	

The main therapeutic strategy for controlling ABPA involves reduction of the hypersensitivity inflammatory reaction to the fungus. The use of the systemic corticosteroid prednisone, and the aerosolised corticosteroids beclomethasone dipropionate and triamcinolone acetonide have proven effective, although their exact modes of action remain unclear.[24,38] However, it is believed that actions include the reduction of bronchial secretions and the inhibition of toxic antibody–antigen inflammatory reactions. The reduction in bronchial secretions provides a less suitable culture medium for the growth of the fungus in the bronchopulmonary tissues.[9,46]

Response to inhaled conidia is an immediate reduction in airflow, followed by recurrent obstruction for four to 10 hours. Initial reduction in airflow is treated with β_2-antagonists, and the recurring symptoms with corticosteroids.[9] A consistent finding is that clinical improvement in 80% of cases is related to decrease in serum IgE levels following corticosteroid treatment.[9] However, the rate of growth in hyphae may be hastened by the presence of cortisone and other drugs,[46] and the use of corticosteroids in cystic fibrosis patients is associated with growth delay, obesity, cataracts and hyperglycaemia.[47,48] Consequently, constant monitoring of specific IgE levels is necessary to guide corticosteroid dosage during ABPA therapy.

In addition to a reduction in IgE level, prednisone will improve lesions seen on chest X-ray and reduce clinical symptoms.[9] Recent work demonstrates the potential of itraconazole as an adjuvant in controlling corticosteroid-dependent ABPA[49] — a significant finding, as it is the first occasion on which an antifungal agent has been used to control an allergic response, although the ability of antibacterial agents to control allergic responses has been noted previously. Subsequently, this finding was confirmed when itraconazole therapy was shown to reduce or eliminate the need for glucocorticoid therapy in ABPA.[50] In addition, the possibility of using cytokines to abolish type-2 T-helper cell (Th2) reactivity and its consequent inflammatory response has been postulated.[48]

More detailed discussion of the therapeutic options available to treat ABPA are beyond the scope of this review and may be found elsewhere.[31]

Invasive aspergillosis

This is the most serious form of aspergillosis as it can lead to disseminated disease, with death occurring within weeks. A substantial majority of patients have pre-existing pulmonary disease.[47] In many of the invasive forms of aspergillosis, necrosis of the airway wall and adjacent pulmonary parenchyma occurs. IA is categorised further into groups, according to the histopathological extension of the fungus into viable tissue.

In immunocompromised patients, infection usually begins in the smaller bronchi and bronchioles, progressing into the larger vessels and alveolar spaces of the lung.[28] Invasive pulmonary aspergillosis (IPA) develops following inhalation of *Aspergillus* spp. conidia. They attach to pulmonary epithelial tissue, germinate, and the hyphae proliferate and expand radially. As they spread, lung tissue dies and visible nodules are formed. Fungal growth is confined to the necrotic tissue, which liquefies and drains via the airways in the cavities seen in sections of lung tissue.[7] This necrotic form of cell death is believed to be due to the release of toxins and enzymes by the fungus.

Early lesions measure 1–3 cm; they show yellow/grey zones of tissue necrosis, and a rim of haemorrhage and thrombosed arteries.[18] It has been suggested that a boundary between necrotic and viable tissue is formed by the action of proteolytic enzymes derived from neutrophils recruited to the site of infection.[7] Invasion is seen only rarely in allergic and saprophytic aspergillosis, and the effects, being focal and minimal, usually are not clinically significant.

Clinical presentation of invasive aspergillosis

In seriously debilitated and immunocompromised patients, the lung is the main source of infection in IA, with fatal consequences despite current therapy.[51] Fraser[7] categorised IA into six classes, many of which have features that overlap (see Table 2); however, acute

Table 2. Various clinical presentations of invasive aspergillosis

Acute bronchopneumonia	Resembles an abscess. Proliferation and invasion of the small membranous and proximal respiratory bronchioles occur. Intense polymorphonuclear leucocyte reaction is associated with necrosis of the airway wall and adjacent pulmonary tissue, which liquefy and drain, producing cavities.
Angio-invasive aspergillosis	Divided into spherical and non-spherical nodule types, the latter being associated with vascular damage and dramatic haemorrhage.
Acute tracheobronchitis	Located predominantly in the tracheobronchial tree, and accounts for 5% of IA. The fungus can form a pseudomembrane that can obstruct the airways or form discrete plaques on the tracheobronchial airway wall. Normally, the fungus invades the tissue surrounding the tracheobronchial wall, and other adjacent tissue.
Miliary aspergillosis	This form shows widespread, random dissemination of minute colonies to all parts of the lung. It occurs in 12% of cases.
Pleural aspergillosis	Uncommon. Local invasion from a fungal plaque in the main bronchus results in the formation of a bronchopleural fistula. Extension from the same site into the main pulmonary artery may cause sudden and massive haemothorax. In some cases, the source of pleural infection may be an aspergilloma.
Chronic necrotising pulmonary aspergillosis	Referred to as 'semi-invasive' aspergillosis, and assigned to slightly immunocompromised individuals. Clinical features are cough, fever, and sputum production, lasting for months or years. Cavitation and fungus-ball formation is different to that seen with aspergilloma because the fungus creates its own cavity through the action of secreted metabolites, causing tissue necrosis.

bronchopneumonia and angioinvasive aspergillosis are the most common.

Diagnosis of invasive aspergillosis

Diagnosis can be difficult and often not made until autopsy.[24] As the clinical presentation of IPA resembles bacterial pneumonia, clinicians usually give antibacterial therapy initially. This clears bacteria but delays correct diagnosis.[18] The consequence of late diagnosis can be irreparable, especially in haematological malignancy and for those on immunosuppressive therapy.

Bronchoscopy, bronchoalveolar lavage (BAL) and histopathology give poor results. Bart-Delabesse *et al.*[52] used a competitive polymerase chain reaction (PCR) technique to detect aspergillus DNA in BAL specimens from AIDS patients but the results were disappointing.

Positive aspergillus cultures from the respiratory tract are found in zero to 56% of cases,[17] and, when isolated from the respiratory tract of granulocytopenic patients with acute leukaemia, are highly suggestive of IA. Direct tissue biopsy is best avoided because of the risk of haemorrhage, but the identification of aspergillus in BAL specimens is a useful indicator of IA.[53] Nasal cultures have been used but are of limited value, particularly in cases of invasive disease.[54]

Although CT scanning is used widely to detect pulmonary infiltrates, and can be more sensitive than standard radiological methods,[55] chest X-ray can detect three types of IPA: cavitation of existing nodules; enlargement of nodules to diffuse pulmonary consolidation; and development of large wedge-shaped, pleural-based lesions that are secondary to vascular invasion by aspergillus and lead to thrombosis and distal necrosis. In addition, it can show fungus ball/mycetoma formation.[19]

Serological methods involve the detection of aspergillus antigens or anti-aspergillus antibodies in patients suspected of having IA, and some success has been achieved. However, a major disadvantage of anti-aspergillus antibody detection is the time required for the patient to develop antibodies to the fungus (days/weeks) and the rapid, lethal progression of IA.[25]

A sandwich enzyme-linked immunoassay to detect aspergillus galactomannan in serum was developed in the mid-1990s and showed promising results in diagnosing IA.[56] Such a development is extremely beneficial because earlier diagnosis will lead to the initiation of antifungal therapy at a stage that will allow containment and clearance of infection, and, therefore, patient recovery. Recent evaluation of the galactomannan immunoassay and PCR methods in a rat model showed that immunoassay was superior in diagnosing and monitoring the development of IA.[57] However, caution should be exercised in translating this finding to the human situation, particularly as the galactomannan immunoassay showed some cross-reactivity with plant carbohydrates, and this could compromise accurate diagnosis.

Treatment of invasive aspergillosis

The major obstacle to the successful treatment of IA is diagnostic delay. Despite many recent technological advances, accurate diagnosis of IA remains difficult; therefore, many patients are diagnosed late in the course of the illness and this impacts on their chances of recovery.[58] Many clinicians feel that aggressive surgical management is one of the best forms of treatment for IPA, but this may be complicated by severe neutropenia.[15]

Conventional treatment relies upon the use of amphotericin B; however, it is characterised by a poor response rate, with a 65% mortality rate recorded in one study.[16] Lower mortality rates have been achieved with itraconazole alone (26%) or in combination with amphotericin B (36%).[16] Drugs such as amphotericin B have many toxic side effects (e.g. nephrotoxicity); thus, clinicians are reluctant to start therapy before microbiological and histopathological confirmation of IA is available.[25]

The efficacy of both aerosolised and liposomal amphotericin B has been evaluated. Although results are incomplete, a decrease in the incidence of infection was seen when the aerosolised form was used,[55] and the liposomal form of the drug has the added benefit of lower toxicity. Itraconazole solution has been evaluated for the treatment of invasive and systemic aspergillosis, with a number of formulations showing potential both in controlling the disease[55] and may have a role in the treatment of infection in neutropenic patients.[59]

The main method of preventing nosocomial IA is the installation of protected environments, and these have had dramatic effect in reducing the incidence of aspergillosis;[16,23,53,60,61] however, infection still can develop if the patient is colonised before admission to hospital.[50,62] Thus, the risk of developing IA is a combination of immunosuppression and the lack of a protective environment.[61] A detailed description of all therapeutic options available for IA is presented elsewhere.[31]

Summary

Pulmonary aspergillosis represents a serious cause of morbidity and mortality in many classes of patient. Those with asthma and cystic fibrosis experience significant fungal colonisation of the lungs due to inherent defects in pulmonary function. Patients receiving

chemotherapy and those with pre-existing lung damage also are susceptible to an increased risk of aspergillosis.

Whilst three main classifications of pulmonary aspergillosis are described in this review, it should be emphasised that disseminated forms of the disease may occur in a minority of cases where immunosuppression is profound.

Existing detection methods rely upon CT and X-ray imaging; however, in the recent past these have been supplemented by the development of immunoassays designed to detect the presence of fungal cell-wall material in serum. Whilst these have been applied to detection, some immunoassay kits have given a high false-positive rate. A robust and reproducible PCR-based assay has yet to emerge that would aid the clinician in detecting aspergillus infection, particularly in cases that do not present significant clinical symptoms.

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