

# Aspergillus-related lung disease

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*Aspergillus* is a ubiquitous dimorphic fungus that causes a variety of human diseases ranging in severity from trivial to life-threatening, depending on the host response. An intact host defence is important to prevent disease, but individuals with pre-existing structural lung disease, atopy, occupational exposure or impaired immunity are susceptible. Three distinctive patterns of *aspergillus*-related lung disease are recognized: saprophytic infestation of airways, cavities and necrotic tissue; allergic disease including extrinsic allergic alveolitis, asthma, allergic bronchopulmonary aspergillosis, bronchocentric granulomatosis and chronic eosinophilic pneumonia; and airway and tissue invasive disease – pseudomembranous tracheobronchitis, acute bronchopneumonia, angioinvasive aspergillosis, chronic necrotizing aspergillosis and invasive pleural disease. A broad knowledge of these clinical presentations and a high index of suspicion are required to ensure timely diagnosis and treatment of the potentially lethal manifestations of *aspergillus*-related pulmonary disease. In the present report, the clinical, radiographic and pathological aspects of the various *aspergillus*-related lung diseases are briefly reviewed.

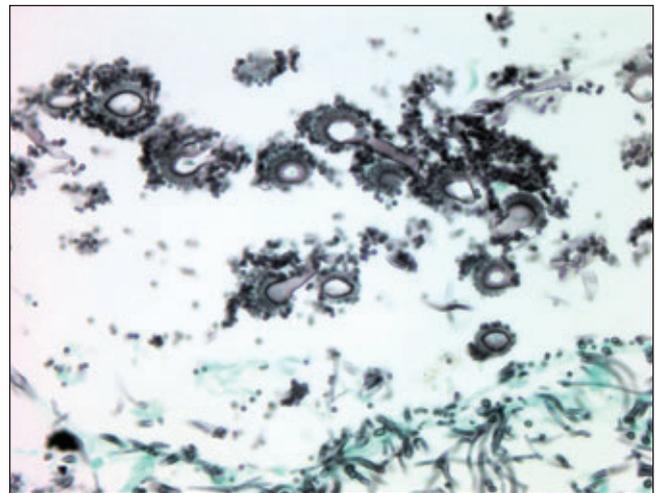
**Key Words:** *Aspergillosis; Aspergillus; Lung disease*

*Aspergillus* is a ubiquitous dimorphic fungus that is present worldwide (1). The fungus is commonly found on stored hay or grain, decaying vegetation, soil, water and various types of organic debris (2). Conidia are present virtually anywhere in the atmosphere and, although disease is uncommon, conidia are inhaled regularly. Many infections are probably derived from general atmospheric contamination, whereas others are related to the presence of organisms in specific sites, including contaminated marijuana cigarettes (3), and such hospital sources as pigeon excreta near ventilation systems and dust created during renovations. Outbreaks of invasive pulmonary aspergillosis in hospital wards have been described in association with hospital reconstruction and renovation (4). More than 300 *Aspergillus* species have been identified, of which only 19 cause human disease (5). The most common species is *Aspergillus fumigatus*, whereas *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus terreus* are infrequently responsible for human infection (6).

The airborne conidia of *A fumigatus* have a diameter small enough (2.5 µm to 3.5 µm) to reach peripheral airways. If the conidia can overcome the immune defence mechanisms in the lung, they germinate and produce branched septate hyphae that invade the lung tissues (Figure 1). The virulence of *A fumigatus*

## Une atteinte pulmonaire reliée à des aspergillus

L'*aspergillus* est un champignon dimorphe ubiquiste responsable de diverses maladies humaines qui peuvent être insignifiantes, mais aussi constituer un danger de mort, selon la réponse de l'hôte. La défense de l'hôte doit être intacte pour prévenir la maladie, mais les individus présentant déjà une atteinte pulmonaire structurelle, une atopie, une exposition professionnelle ou une atteinte immunitaire y sont prédisposés. Trois modèles distincts d'atteinte pulmonaire reliée à des *aspergillus* sont comptabilisés : l'infestation saprophytique des voies respiratoires, des cavernes et du tissu nécrotique, une atteinte allergique incluant la pneumopathie d'hypersensibilité, l'asthme, l'aspergillose bronchopulmonaire allergique, la granulomatose bronchocentrique et la pneumonie à éosinophiles chronique ainsi qu'une atteinte invasive des tissus et des voies respiratoires telle que la trachéobronchite pseudomembraneuse, la bronchopneumonie aiguë, l'aspergillose envahissant les vaisseaux sanguins, l'aspergillose nécrosante chronique et l'atteinte pleurale invasive. Des connaissances sur ces présentations cliniques et un fort indice de présomption sont nécessaires pour garantir le diagnostic et le traitement rapides des manifestations au potentiel mortel d'une atteinte pulmonaire reliée à des *aspergillus*. Dans le présent rapport, les aspects cliniques, radiographiques et pathologiques des diverses atteintes pulmonaires reliées à des *aspergillus* sont brièvement passés en revue.



**Figure 1)** High-power photomicrograph (methenamine silver stain) showing *aspergillus* fruiting heads (conidiophores with sterigmata and conidia), which sometimes form in cavities that communicate with the atmosphere, thus exposing the organism to air. Branching fungal hyphae are also shown in the lower part of the image

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**TABLE 1**  
**The spectrum of aspergillus-related lung disease**

<b>Saprophytic infestation</b>
Simple colonization
Aspergilloma
Invasion of necrotic tissue
<b>Allergic disease</b>
Extrinsic allergic alveolitis
Asthma
Allergic bronchopulmonary aspergillosis
Bronchocentric granulomatosis
Chronic eosinophilic pneumonia
<b>Invasive aspergillosis</b>
Pseudomembranous tracheobronchitis
Acute bronchopneumonia
Angioinvasive aspergillosis
Chronic necrotizing aspergillosis
Invasive pleural disease

is probably related to the production of fungal proteins that promote mycelial growth into the lung parenchyma, or to structural features of the conidia that confer resistance to the host's antifungal mechanisms (7). *Aspergillus* species produce a variety of toxic substances that are thought to be important in the pathogenesis of disease. These substances include endotoxins that have been shown to inhibit epithelial ciliary activity and a variety of proteases, including elastase, collagenase and trypsin, that can damage the epithelial tissue. The risk of developing disease depends on the interplay between the organism's virulence and the host's ability to resist infection. In addition to the host immune status, the other major factor that determines the resulting type of aspergillus reaction is the initial state of the lung parenchyma.

The first line of host defence against aspergillus is the respiratory tract epithelium, with the majority of *A fumigatus* conidia being extruded from the lung by the ciliary action of the mucous epithelium. In situations where such clearance appears to be deranged, as in bronchiectasis or in the cavities of chronic tuberculosis, the likelihood of fungal colonization and growth is greatly increased. Pulmonary macrophages and neutrophils constitute another important line of host defence (8). Large doses of corticosteroids inhibit the killing of conidia and hyphae by macrophages and inhibit migration of neutrophils around the fungus (9). Neutropenia is a major risk factor for invasive aspergillosis (10). In recent years, it has been shown that T-cell immunity and associated cytokines and/or chemokines have a role in the control of *A fumigatus* infection (11,12).

In tissue, aspergillus typically grow as regular septate hyphae, with characteristic dichotomous branching at 45° angles, which can usually be observed with hematoxylin and eosin stains, but are best observed with periodic acid-Schiff or Gomori's methenamine silver stains (Figure 1). Although aspergillus can infect virtually any organ, the lung is by far the most commonly affected. Within the lung, a spectrum of disease exists depending on the host's immune status, ranging from colonization of the airways in the immunocompetent patient to tissue invasion by the fungus in the severely immunocompromised patient. Although discrete syndromes have been described, there is some

degree of overlap, perhaps reflecting the variability of immune response mounted by the host. Three distinctive patterns of aspergillus-related lung disease are recognized: saprophytic infestation of airways, cavities and necrotic tissue; allergic disease including extrinsic allergic alveolitis, asthma, allergic bronchopulmonary aspergillosis (ABPA), bronchocentric granulomatosis and chronic eosinophilic pneumonia; and airway and tissue invasive disease – pseudomembranous tracheobronchitis, acute bronchopneumonia, angioinvasive aspergillosis, chronic necrotizing aspergillosis and invasive pleural disease (Table 1).

## PULMONARY SYNDROMES RELATED TO ASPERGILLUS

### Saprophytic infestation

**Simple colonization:** Aspergillus can exist on body surfaces and in bronchi without eliciting a pathological response (13). It is particularly common in patients with underlying airway disease such as cystic fibrosis, asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis. Tissue invasion is not a feature of colonization, although pulmonary aspergillosis can develop if host defence is altered.

**Aspergilloma:** Saprophytic colonization of a parenchymal cavity by a fungus is termed a mycetoma or fungus ball, or in the case of *Aspergillus* species, an aspergilloma. A fungus ball consists of a grossly identifiable cluster of intertwined hyphae matted together with a variable amount of mucus and cellular debris (7). It typically occurs in ectatic airways or parenchymal cavities. Conditions associated with aspergilloma formation include tuberculosis (14-24); sarcoidosis (18-28); histoplasmosis (18); lung abscess (14,20-24); bronchiectasis (17,18,20,21); lung cancer (17,23,28); bullae (17,20,26,28); postradiation fibrosis (21,22,24,28); pulmonary infarcts (20,28); cavities associated with rheumatoid arthritis, ankylosing spondylitis and Wegner's granulomatosis (20,21,24,28,29); cystic fibrosis (30,31); allergic bronchopulmonary mycosis (20,31); and HIV infection (32,33).

Up to 50% of patients with pulmonary aspergilloma can be asymptomatic (22). Hemoptysis, occasionally massive and life threatening, is the most common clinical presentation, occurring in 74% of patients in one series (34). Other clinical features include cough and bronchorrhea, fever, weight loss and dyspnea. Plain chest radiographs classically show a mass within a cavity. Computed tomography (CT) characteristically shows an intracavitary mass with a surrounding air crescent most commonly in the upper lobes (Figure 2). The aspergilloma may move when the patient changes position (35). Thickening of the adjacent pleura is frequent. Positive sputum cultures for *Aspergillus* species can be seen in 58% of patients (23), with *A niger* being the most commonly identified type (25,28). Sputum cultures, however, are of minor diagnostic value due to the ubiquitous presence of the fungus. Virtually all patients with an aspergilloma have precipitating antibodies to aspergillus antigens in their serum (36).

Treatment of aspergilloma remains problematic. Antifungal agents have been used with limited success. Nebulized antifungals have not been shown to reduce the size of the aspergilloma (20,21). Systemic antifungals have led to no change or minimal reduction in the size of the fungus ball (20,24,37). In fact, Hammerman et al (38) showed that intravenous administration of amphotericin B is no more effective than a pulmonary toilet regimen in the management of patients with aspergillomas. Intracavitary or endobronchial instillation of antifungal

agents has also been attempted with variable outcomes (20,23,26,39-45); these measures may stop life-threatening hemoptysis and improve clinical symptoms. Corticosteroid therapy may improve symptoms (20) but carries the risk of dissemination or enlargement of the fungus ball. Radiotherapy has been shown to control hemoptysis (46). Medical treatment is appropriate for symptomatic patients who are poor surgical candidates on account of their underlying disease.

Surgical resection of the affected lung is the definitive treatment for an aspergilloma. Unfortunately, surgery is associated with considerable morbidity (25%) and mortality (8% to 10%) (22), and many patients are unsuitable because of limited pulmonary reserve. Postoperative complications include empyema, bronchopleural fistula, hemorrhage and infection including disseminated fungal infection. Some authors advocate prophylactic surgical treatment (47,48), whereas others reserve it for symptomatic patients, mainly those with hemoptysis (20,22,25). The unpredictable course of the illness in the absence of surgery confounds decisions about surgical intervention (49).

**Invasion of necrotic tissue:** Invasion of necrotic tissue is a rare form of aspergillus lung disease that manifests as colonization of nonviable lung parenchyma resulting from necrotizing pneumonia (lung gangrene) (50), pulmonary infarction (51) or a necrotic tumour (52). Unless the patient is immunocompromised, invasion of viable lung tissue does not occur.

#### Allergic disease

**Extrinsic allergic alveolitis:** Extrinsic allergic alveolitis, most likely the result of a hypersensitivity reaction to inhaled conidia, occurs after intense exposure to different *Aspergillus* species including *A fumigatus*, *Aspergillus clavatus* (53-55) and *Aspergillus versicolor* (56). It is usually seen in an occupational setting, especially among whiskey distilling and beer-brewing workers. Extrinsic allergic alveolitis caused by *A clavatus* is called malt-worker's lung (53,54). Dog house disease is attributed to *A versicolor* (56). Cases of farmer's lung caused by *A fumigatus* have also been reported (57). Immunological evidence suggests that the disease is caused by either a type III or IV hypersensitivity response or a combination of both (58). Clinically, the illness may be insidious or acute in presentation depending on the intensity of exposure to the responsible antigen (59). Common presenting features include malaise, sweating, chills, myalgia, anorexia, dyspnea and a sense of tightness in the chest. Serum precipitins to aspergillus extracts are usually present (60). Spontaneous resolution of the acute lung changes may follow removal of the patient from further exposure. Corticosteroids are given to very ill patients and may lead to prompt resolution of the illness.

**Allergic asthma:** Allergic asthma is a type I hypersensitivity reaction that occurs in atopic individuals. It is more common between October and February when aspergillus spore counts are high (60). A skin test using aspergillus antigen produces an immediate reaction; however, this test lacks specificity. Bronchoprovocation with aspergillus antigen is usually positive. Precipitating antibodies are usually absent in such patients. Bronchodilators and inhaled corticosteroids are the treatment of choice (60).

**ABPA:** ABPA is a hypersensitivity reaction to *A fumigatus* that occurs in patients with asthma or cystic fibrosis. Its prevalence in asthmatic patients ranges from 3% to 16% (61,62) and, in cystic fibrosis patients, from 2% to 8% (63-66). ABPA has also been reported in cystic fibrosis patients after undergoing



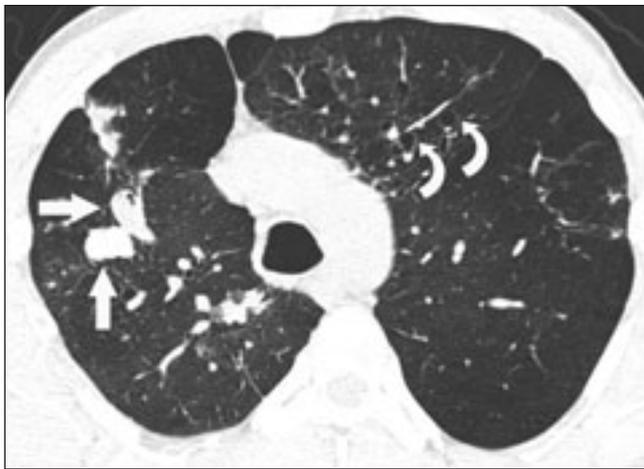
**Figure 2** High-resolution computed tomography of the chest performed with the patient prone showing mycetoma within a left upper lobe cavity. Also shown is extensive pleural thickening. The patient was a 58-year-old man with chronic upper lobe scarring and bronchiectasis due to previous tuberculosis

lung transplantation (67). ABPA is characterized by inspissated mucous plugs containing aspergillus organisms and eosinophils resulting in chronic inflammation in the airway wall and bronchial ectasia. Patients develop recurrent episodes of wheezing, malaise, low-grade fever, cough, sputum production, hemoptysis, chest pain and pulmonary infiltrates. They may have a history of poorly controlled asthma, recurrent pneumonia and frequent antibiotic therapy. Regional lymphadenopathy associated with ABPA has been described (68,69).

On plain radiographs, the characteristic pattern is finger-like, homogeneous, branching opacities usually involving the segmental and more central subsegmental bronchi of the upper lobes (35). These findings are related to plugging of airways by hyphal masses with distal mucoid impaction (70). Mucous plugs may resolve quickly or last for a number of months. Resolution of the plugging may reveal residual, typically central, bronchiectasis, and bronchial wall thickening. These manifest as ring shadows or linear 'tram tracks' on the chest radiograph (35). The most common CT finding is central bronchiectasis with upper lobe predominance (Figure 3). Bronchiectasis affecting three or more lobes, centrilobular nodules and mucoid impaction are findings highly suggestive of ABPA (71). In approximately 30% of patients, the impacted mucus has high attenuation or demonstrates frank calcification on CT (70).

Bronchoscopy has been shown to have a role in the diagnosis of ABPA (72,73), especially in patients with atypical manifestations and those who do not meet the standard diagnostic criteria (see below). Bronchoscopic examination in these two studies (72,73) revealed evidence of mucous plugging. Histological examination of the mucous plugs showed that they consisted of so-called 'allergic mucin' containing fungal hyphae and eosinophils.

On histological examination, proximal airways containing mucous plugs are usually ectatic and inflamed. Eosinophils and plasma cells predominate and the airway epithelium is usually intact. Fungal invasion of the bronchial wall is almost never seen. Mucous plugs typically contain numerous eosinophils and Charcot-Leyden crystals, and have a laminated, somewhat



**Figure 3)** High-resolution computed tomography showing mucoid impaction (straight arrows) in the right upper lobe and varicose bronchiectasis (curved arrows) in the left upper lobe. The patient was a 54-year-old man with asthma and allergic bronchopulmonary aspergillosis

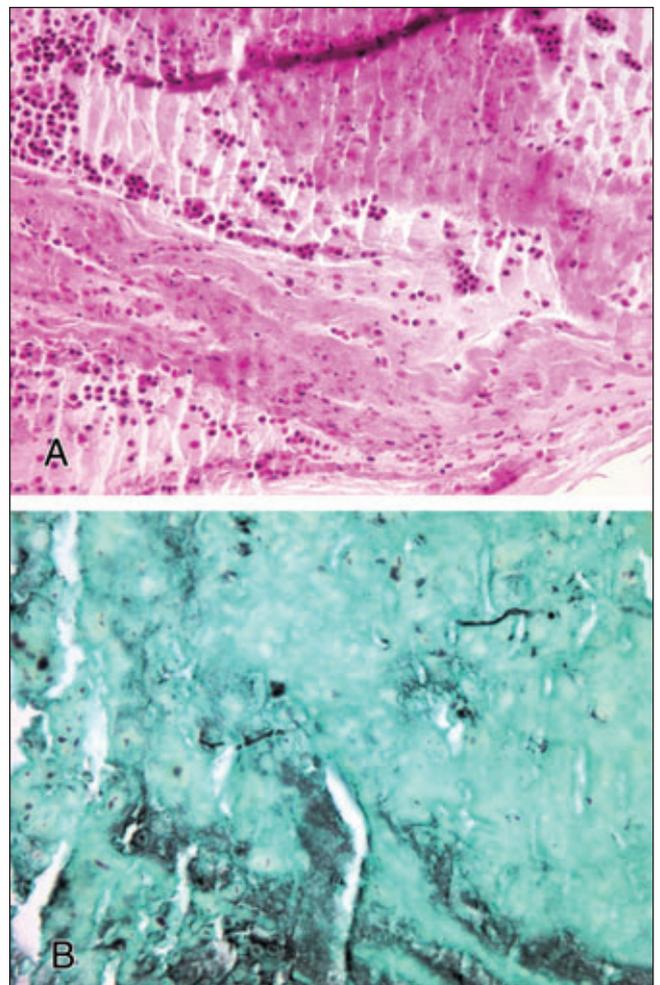
geometric appearance (Figure 4A). Fungal hyphae, often fragmented and sometimes swollen and degenerated in appearance, are difficult to identify on hematoxylin and eosin-stained sections, but usually can be readily seen with a silver stain (Figure 4B). Bronchocentric granulomatosis (see below) is another occasional histological abnormality seen in ABPA (7).

The diagnosis of ABPA is established using clinical, immunological and radiographic criteria (74). The major and minor diagnostic criteria are listed in Table 2. The presence of all major criteria confirms the diagnosis, and the presence of six criteria make the diagnosis of ABPA highly likely.

Five stages of the disease have been proposed:

- Stage I (acute stage) is associated with asthma, fever and productive cough with blood eosinophilia and pulmonary infiltrates. This stage is completely reversible with corticosteroids.
- Stage II (remission) is asymptomatic and associated with a normal chest radiograph and decreased serum immunoglobulin (Ig) E and eosinophilia.
- Stage III (recurrent exacerbation) is characterized by recurrence of the same findings of stage I in association with doubling of serum IgE concentrations.
- Stage IV (steroid-dependent) is characterized by symptomatic asthma requiring corticosteroid therapy for control.
- Stage V (fibrotic) is characterized by severe dyspnea, pulmonary fibrosis and a mixed obstructive/restrictive pattern on pulmonary function testing (75,76).

Treatment of ABPA aims at relieving the acute exacerbations and preventing progressive lung damage. Early recognition and aggressive treatment of the early stages may halt progression. Corticosteroids are the cornerstone of treatment; however, most of the supportive data come from uncontrolled trials. Rosenberg et al (77) showed resolution of symptoms and active roentgenographic infiltrates when patients were administered prednisone 0.5 mg/kg body weight daily. Patients may need to



**Figure 4)** High-power photomicrographs of mucoid impaction in a patient with allergic bronchopulmonary aspergillosis. **A** Hematoxylin and eosin stain showing the laminated appearance of allergic mucin containing abundant eosinophils, eosinophilic debris and Charcot-Leyden crystals. **B** Methenamine silver stain showing degenerating aspergillus hyphae within inspissated mucus

be maintained on low-dose corticosteroids after remission is achieved. In the same study, pulmonary infiltrates recurred in a few patients while they were receiving full maintenance alternate day prednisone. A 10 mg daily dose of prednisone may be needed to prevent the recurrence of pulmonary infiltrates (78). Antifungal agents may have a role in the treatment of ABPA. A recent Cochrane review (79) concluded that itraconazole modifies the immunological activation associated with ABPA and improves clinical outcome, at least over the 16 weeks of treatment. Fifty patients with corticosteroid-dependent ABPA were randomly assigned to treatment with itraconazole 200 mg twice daily or placebo for 16 weeks (80). The study showed a reduction of corticosteroid dose, a decrease in serum IgE level, an improvement in pulmonary function and resolution of pulmonary infiltrates in 46% of patients compared with 19% in the placebo group. Another randomized controlled trial (81) found that treatment of stable ABPA with itraconazole 400 mg daily reduced airways eosinophilic inflammation, systemic immune activation and exacerbations. A few other nonrandomized studies (82-84) showed similar effects of

**TABLE 2**  
**Allergic bronchopulmonary aspergillosis – diagnostic criteria**

**Major criteria**

- A history of asthma
- Immediate skin test reactivity to aspergillus
- Precipitating serum antibodies to *Aspergillus fumigatus*
- Serum total IgE concentration greater than 1 µg/mL
- Peripheral blood eosinophilia >500/mm<sup>3</sup>
- Lung infiltrates
- Central bronchiectasis
- Elevated specific serum IgE and IgG to *A fumigatus*

**Minor criteria**

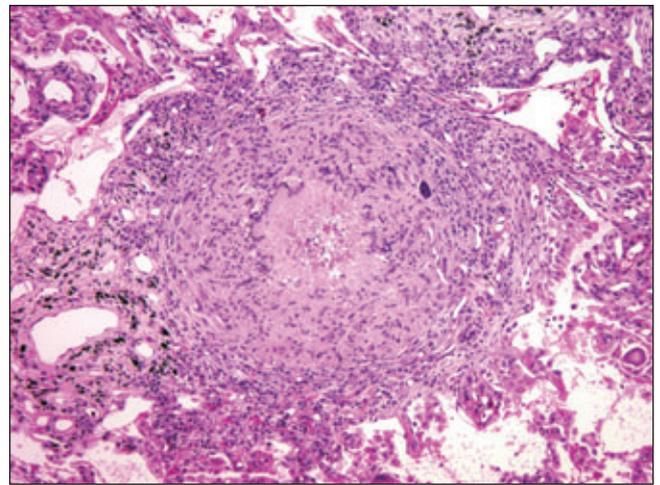
- A fumigatus* in sputum (by repeated cultures or microscopic examination)
- History of expectoration of brown plugs or flecks
- Arthus reactivity (late skin reactivity) to aspergillus antigen

*Ig Immunoglobulin*

itraconazole in asthmatic and cystic fibrosis patients with ABPA. Itraconazole may therefore have a steroid sparing effect and play a role in steroid-dependent patients or those who refuse to take corticosteroids. Nebulized natamycin, however, did not confer any benefit when given to patients with steroid-dependent ABPA (85). Inhaled corticosteroids were shown to have no effect on the episodes of pulmonary eosinophilia; however, the control of asthma symptoms was improved by the addition of beclomethasone treatment to maintenance therapy (86). Imbeault and Cormier (87) demonstrated a steroid sparing effect of high-dose inhaled corticosteroids when used by two steroid-dependent ABPA patients. A study by Seaton et al (88) concluded that the use of inhaled corticosteroids is safe and effective in the management of ABPA when diagnosed before the occurrence of hyphal colonization of the airways.

Obstructing bronchopulmonary aspergillosis is a form of noninvasive aspergillosis characterized by a massive overgrowth of *Aspergillus* species in the airways of patients with AIDS (89,90). Although this condition shares some of the clinical and radiographic features of ABPA, the finding of tracheobronchial pseudomembranes on bronchoscopy suggests some overlap with pseudomembranous tracheobronchitis, a form of invasive aspergillosis discussed below.

**Bronchocentric granulomatosis:** Bronchocentric granulomatosis is a destructive granulomatous disease of the bronchi and bronchioles that occurs as a nonspecific reaction to airway injury (91). In approximately 50% of cases it occurs in the context of ABPA and is thought to be a hypersensitivity reaction to aspergillus (92). Peribronchiolar necrotizing granulomas cause destruction of airways and adjacent parenchyma (Figure 5). There is often associated mucoid impaction, eosinophilic pneumonia and fungal invasion of the surrounding parenchyma. The clinical features are those of ABPA. Occasionally, bronchocentric granulomatosis is the predominant histological pattern in chronic necrotizing aspergillosis, a form of invasive aspergillosis discussed below. Single or multiple pulmonary nodules are apparent radiographically (93). Excisional biopsy is required for the diagnosis but has not been shown to provide benefit. Some patients respond to corticosteroid therapy (92).



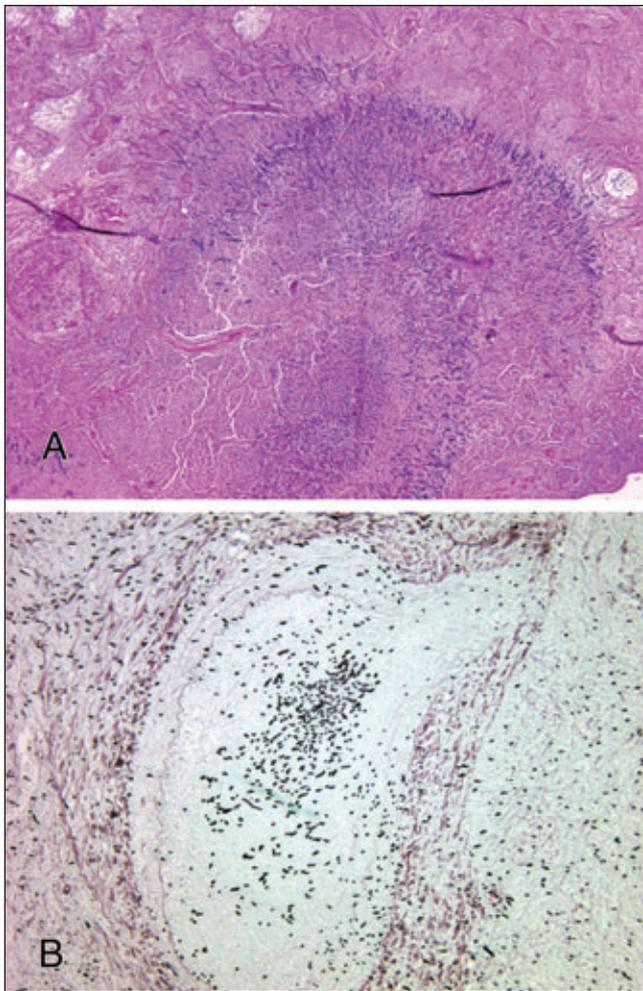
**Figure 5)** Medium-power photomicrograph showing necrotizing granulomata consisting of palisaded histiocytes and giant cells surrounding a necrotic bronchus containing fungal hyphae. The patient had bronchocentric granulomatosis due to aspergillus infection

**Chronic eosinophilic pneumonia:** *Aspergillus* has rarely been implicated as a cause of chronic eosinophilic pneumonia (94,95). Patients present with the typical features of cough, dyspnea, fever and pulmonary infiltrates in a peripheral distribution. Histopathological features and response to corticosteroids are similar to those of other forms of this condition (94).

**Invasive aspergillosis**

Invasive aspergillosis, occurring in immunocompromised patients, is the most serious category of aspergillus-related lung disease because it can lead to disseminated disease and death within weeks. Predisposing conditions include bone marrow transplantation and hematological diseases such as leukemia or lymphoma (96), solid organ transplantation (97), solid tumours, chronic granulomatous disease (96), AIDS (96,98,99) and patients treated with corticosteroids (100-102). Invasive aspergillosis occurs in several forms including tracheobronchial aspergillosis, acute bronchopneumonia, angioinvasive aspergillosis and chronic necrotizing (semi-invasive) aspergillosis.

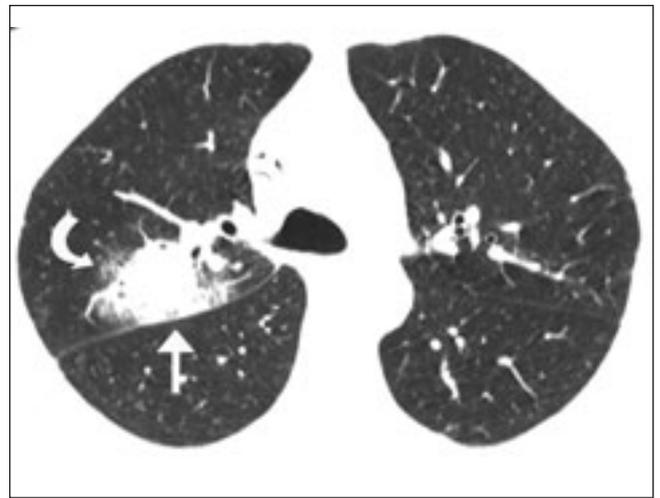
**Pseudomembranous tracheobronchitis:** *Aspergillus* tracheobronchitis is an uncommon manifestation of acute aspergillus infection, occurring in approximately 5% of cases of invasive aspergillosis (103). Infection is confined to the larger airways, often with the formation of inflammatory pseudomembranes. Although unproved, it is suggested that aspergillus tracheobronchitis is more common in mildly to moderately immunocompromised patients, perhaps explaining its endobronchial location (104). There is a particular association with heart or heart-lung transplantation. In single-lung transplant recipients, infection may be confined to the transplanted side at the site of the bronchial anastomosis (105). In patients with COPD, infection has also been reported as a complication of the treatment of exacerbations with broad spectrum antibiotics and corticosteroids (100,106). Histologically, there is focal or diffuse ulcerative tracheobronchitis with pseudomembranes, mucous plugs and fungal hyphae with superficial mucosal invasion and intense submucosal inflammation. Patients with aspergillus tracheobronchitis may be asymptomatic initially.



**Figure 6** Medium-power photomicrographs showing invasive aspergillosis. **A** Hematoxylin and eosin stain showing tissue invasive aspergillosis with fungal hyphae growing radially in concentric layers, and an adjacent area of hemorrhagic pulmonary infarction (top left of image). **B** Methenamine silver stain showing angioinvasive aspergillosis with a blood vessel occluded by a mass of aspergillus organisms

The most common presenting complaints are cough, fever, dyspnea, chest pain and hemoptysis (103). Patients occasionally expectorate intraluminal mucous plugs or tracheobronchial casts. The chest radiograph may be unremarkable unless there is associated bronchopneumonia or atelectasis (35). High-resolution CT typically shows centrilobular nodules and a 'tree-in-bud' appearance (70), corresponding to dilated and impacted bronchioles imaged parallel or perpendicular to the imaging plane.

**Acute bronchopneumonia (airway-invasive aspergillosis):** Various histological patterns of acute aspergillus bronchopneumonia have been reported, including patchy ill-defined nodules centred around terminal bronchioles, sharply circumscribed small nodules with central cavitation, confluent airspace disease or larger nodules (7,107). Occasionally, this pattern is seen in association with pseudomembranous tracheobronchitis, and vascular invasion can occur, suggesting that in terms of invasive behaviour, bronchopneumonia is intermediate between tracheobronchitis and angioinvasive disease. Patients typically



**Figure 7** High-resolution computed tomography showing right upper lobe nodule (straight arrow) immediately anterior to the major fissure. Areas of ground glass attenuation (curved arrow) are seen adjacent to the nodule (computed tomography 'halo sign'). The patient was a 46-year-old man with acute myelogenous leukemia and angioinvasive aspergillosis

present with high fever progressing to respiratory failure if the disease is extensive. The chest radiograph shows patchy or confluent airspace disease or ill-defined nodules. The chest CT shows centrilobular nodules, a tree-in-bud pattern or consolidation in a peribronchial distribution (89,108).

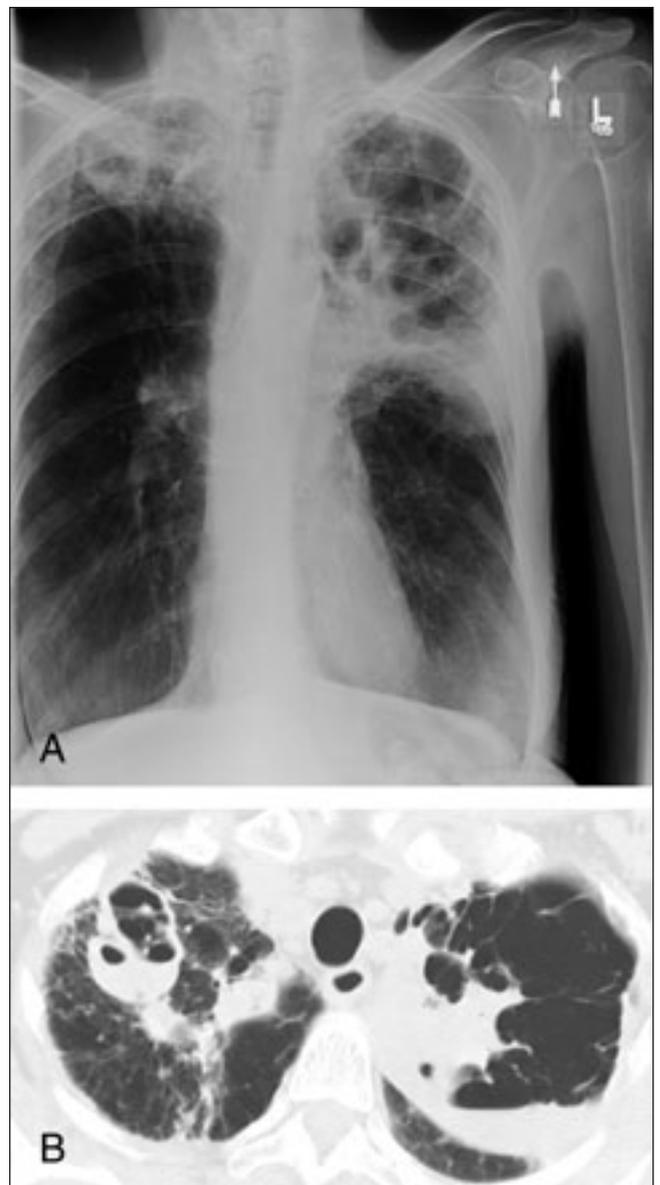
**Angioinvasive aspergillosis:** There are two histological variants of angioinvasive aspergillosis: a nodular variety (Figure 6A) and a disease caused by vascular damage (Figure 6B) producing pulmonary infarcts similar to those due to bland pulmonary emboli (7). Patients present with fever, dyspnea, nonproductive cough and pleuritic chest pain (1). The radiographic appearance reflects the previously mentioned pathological patterns. The initial abnormality consists of one or more subtle nodular opacities that may be overlooked. Typically, chest radiographs show rapid progression of these nodular opacities to form single or multiple areas of homogeneous consolidation (109). These lesions may show a characteristic 'halo sign' seen on CT (Figure 7) reflecting an area of alveolar hemorrhage surrounding a central nodule. The nodules with halos often progress to form air crescents that indicate necrotizing pneumonia (35). Other manifestations include wedge-shaped pleural-based areas of consolidation reflecting the presence of subsegmental or segmental infarcts (35).

Although early recognition and therapy with antifungal agents appear to improve survival, early diagnosis is difficult. Definitive diagnosis requires biopsy from an involved organ yielding both histopathological evidence of acutely angled, branching, septated, nonpigmented hyphae measuring 2  $\mu$ m to 4  $\mu$ m in width and positive cultures yielding *Aspergillus* species (49); these criteria may not be attainable in very ill patients. The isolation of *Aspergillus* species from respiratory tract specimens in high-risk patients, especially leukemic or neutropenic patients, is a significant predictor of invasive disease (110,111). Combined fungal stains and cultures have a sensitivity of 32% to 58% and a specificity of 92% to 99.7% (112,113). Bronchoscopy yields a diagnosis in 22% to 30% of cases (113,114).

Several tests have been developed to detect aspergillus antigens, including galactomannan, using enzyme immunoassay (115,116), immunoblot (117) and ELISA techniques (118). Maertens et al (119) found that detection of galactomannan antigenemia had 94% sensitivity and 99% specificity for the diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. Positive serology preceded radiographic abnormalities by eight to nine days in over 80% of patients. Tests are also available to detect aspergillus antibodies (120,121); however, these tests depend on a normal host immune response, which is absent in immunosuppressed patients. A polymerase chain reaction test to detect DNA of *Aspergillus* species has been developed (122-124).

Successful therapy of invasive aspergillosis depends on early diagnosis and prompt initiation of treatment because delay is associated with a high fatality rate. Therefore, treatment should be started empirically, without awaiting definitive diagnosis in patients suspected of having invasive pulmonary aspergillosis. Amphotericin B is currently the drug of choice for the treatment of invasive aspergillosis (125,126). It should be given at a dose of 1 mg/kg/day to 1.5 mg/kg/day (39). The overall response rate to amphotericin B is 37%, with a range of 14% to 83% (127). Liposomal amphotericin B has been shown to be efficacious and safe, and it causes fewer nephrotoxic side effects (128,129). It is reserved for patients who develop nephrotoxicity while receiving amphotericin B (49), and for those with marginal renal function or patients receiving other nephrotoxic medications (128-134). Response rates to itraconazole have been reported to be similar to those of amphotericin B (24,135,136). In a large nonrandomized study (136), itraconazole resulted in a complete or partial response in 39% of patients, with 26% failing to respond. The absorption of itraconazole is unreliable in seriously ill patients with disturbed gastrointestinal function (137). Furthermore, itraconazole interacts with several medications. A logical therapeutic sequence would be to use intravenous amphotericin B first, stepping down to oral itraconazole for prolonged treatment (49). Voriconazole is a more recent triazole compound that has activity against aspergillus. In a multicentre randomized open-label study (138), intravenous voriconazole had a greater likelihood of producing a complete or partial response, lower mortality and lower rates of several adverse reactions compared with intravenous amphotericin B. Although there are concerns about instances of breakthrough infections with yeasts and molds with reduced susceptibility to voriconazole (139), it is increasingly recommended as the initial therapy for invasive aspergillosis. The recommended regimen for voriconazole is 6 mg/kg 12 hourly for two doses followed by a maintenance dose of 4 mg/kg 12 hourly, stepping down to 200 mg orally twice daily. More recent antifungal agents such as caspofungin and micafungin are currently under study and have shown efficacy in animal models and case reports in humans (140-142). Treatment of invasive aspergillosis should be prolonged beyond clinical resolution of the disease and correction of any potentially reversible underlying predisposing conditions.

Despite treatment with antifungal agents, mortality associated with invasive pulmonary aspergillosis continues to be high, ranging from 50% to 93% depending on the underlying disease (127). Surgical resection, in combination with antifungal agents, has been shown in some instances to be effective in the treatment of invasive aspergillosis (143,144). Several adjuvant therapies are under study. These include interferon gamma



**Figure 8** (A) Chest radiograph and (B) high-resolution computed tomography showing chronic necrotizing or semi-invasive aspergillosis. There is dense consolidation in the left upper lobe and focal consolidation in the right upper lobe, as well as an air-fluid level in a right upper lobe bulla. Computed tomography improves visualization of the underlying upper lobe emphysema. The patient was a 75-year-old woman with chronic obstructive pulmonary disease. The radiographic findings progressed over six months. *Aspergillus* species was the only pathogen grown on several cultures

(145), granulocyte colony-stimulating factor (CSF) (146), macrophage-CSF (147) and granulocyte transfusions (148). Improved survival has not been reported with any of these modalities. Some preventive strategies to reduce the risk of contracting invasive aspergillosis in high-risk patients include reduction of exposure to aspergillus by the use of high-efficiency particulate air filters (149), prophylactic nebulized amphotericin B (150), systemic amphotericin B (151) or systemic azoles (152,153), and administration of granulocyte-CSF to shorten the period of neutropenia (149).

**Chronic necrotizing aspergillosis:** Semi-invasive aspergillosis, also known as chronic necrotizing aspergillosis, has recently been recognized as a different type of infection that does not fit into traditional categories. It runs a more indolent course, occurring in patients with mildly impaired immunity. Among the conditions associated with the development of semi-invasive aspergillosis are COPD, diabetes mellitus, poor nutrition, alcoholism, connective tissue disease and treatment with corticosteroids (154,155). The most common presenting complaints are fever, cough, sputum production (154) and weight loss (155). Symptoms may relate to the underlying lung disease, but the fungus is thought to be responsible for the slowly progressive tissue destruction. The duration of symptoms before the institution of therapy ranges from one month to greater than two years (154). The radiographic findings consist of upper lobe consolidation, multiple nodules (156) and cavitory disease (154) (Figure 8). Pathological patterns include necrotizing granulomatous pneumonia, granulomatous bronchiectatic cavities and bronchocentric granulomatosis. Chronic necrotizing aspergillosis is occasionally confined to the airways without evidence of extension into the lung parenchyma (89). Antifungals are the mainstay of treatment (154,155). Itraconazole, with a response rate of 90%, is the most effective

therapy currently available (155). Intravenous and intracavitary amphotericin B and 5-fluorouracil have also been used, with the highest response rates obtained with intracavitary amphotericin B (155).

**Invasive pleural disease:** The pleural space occasionally becomes infected with aspergillus. Most commonly this occurs in patients who have undergone artificial pneumothorax therapy for pulmonary tuberculosis (157). Presumably, the organism gains entry to the pleural space from colonization or infection of adjacent damaged lung parenchyma. Pleural aspergillosis can also complicate lobectomy or pneumonectomy for tuberculosis or lung cancer, and is usually accompanied by a bronchopleural fistula (158). Pleural involvement either as direct invasion of the pleural cavity or as pleural fibrosis has been reported as a complication of chronic cavitory and fibrosing pulmonary aspergillosis (159). Although rare, infection of the pleural space may occur in the setting of disseminated aspergillosis (160). Clinical features are those of an acute or chronic empyema. Radiographs typically show pleural thickening and an air-fluid level. Treatment consists of extensive surgical debridement, systemic antifungal therapy and, occasionally, intrapleural instillation of antifungal agents together with prolonged drainage.

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