
New clinical presentations of invasive aspergillosis in non-conventional hosts

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ABSTRACT

Infections by *Aspergillus* spp. are most typically associated with invasive pulmonary aspergillosis. However, an increasing number of reports deal with unusual manifestations of invasive aspergillosis. In the lung this may take the form of chronic invasive pulmonary aspergillosis, bronchocentric granulomatosis or tracheobronchitis. A number of extrapulmonary infections have been noted, sometimes in immunocompetent individuals. Examples include vertebral osteomyelitis, primary cutaneous aspergillosis (such as in premature neonates), prosthetic vascular graft infection and infective endocarditis. Early recognition of these entities, prompt initiation of new, highly active antifungal therapies and adjunctive surgical management may improve the prognosis of these conditions.

Keywords *Aspergillus*, transplantation, endocarditis, vertebral osteomyelitis

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INTRODUCTION

Invasive aspergillosis has classically been associated with pulmonary infection. Invasive pulmonary aspergillosis is the most common manifestation of serious aspergillus infection in all hosts. Other pulmonary manifestations include aspergilloma or allergic bronchopulmonary aspergillosis. This paper will not discuss these conditions but instead will focus on a number of extrapulmonary manifestations and some rare pulmonary manifestations of invasive aspergillosis (Table 1).

ASPERGILLUS VERTEBRAL OSTEOMYELITIS

Aspergillus spp. may occasionally infect bone [1–48]. The most commonly reported site of

Table 1. Classical and emerging clinical presentations of invasive aspergillosis

Classical presentations

Acute invasive pulmonary aspergillosis
Aspergillus invasive sinusitis
Disseminated infection, including cerebral aspergillosis

Emerging extrapulmonary infections

Primary cutaneous aspergillosis
Aspergillus osteomyelitis
Vascular graft infection

Emerging pulmonary infections

Tracheobronchitis
Chronic invasive pulmonary aspergillosis

infection has been the spine. Of reported cases, the lumbar vertebrae were infected in 53% of cases, the thoracic vertebrae in 46% of cases and the cervical vertebrae in just 2% of cases [20]. A surprisingly high proportion of patients (34%) have no underlying immunocompromise [20]. Some of these patients had a history of previous laminectomy and discectomy. Those with underlying immunocompromise had been receiving corticosteroids, chemotherapy, or transplant immunosuppression or had neutropenia or chronic granulomatous disease. Presumably most cases

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arise from haematogenous spread from a distant site, but a few cases have occurred from direct extension from a pulmonary or aortic focus. There is a bimodal age distribution amongst reported cases—children with chronic granulomatous disease and then older adults with other underlying disorders.

Back pain is an almost universal initial symptom of vertebral osteomyelitis caused by *Aspergillus* spp. Unfortunately some patients have presented with paraparesis [20]. The neurological prognosis for patients who present with paraparesis is extremely poor. Surprisingly few patients have elevated peripheral white blood cell count (just 28% of those reported have had a white blood cell count greater than 11 000/mm³) [20]. However, the majority have an elevated erythrocyte sedimentation rate (although occasional patients have been noted with an erythrocyte sedimentation rate less than 40 mm/h).

The clinical approach to aspergillus vertebral osteomyelitis depends on age, underlying medical conditions and evidence of structural instability or neural compression. When spinal instability or symptoms of spinal cord or radicular compression are present, surgical decompression is indicated [20]. The type and extent of surgery should be individualised; some patients may merely require percutaneous needle aspiration while others will require laminectomy with abscess drainage or debridement, with or without autologous bone grafting. Systemic antifungal therapy should be administered in all cases. The mortality rate from reported cases has been 26.8% [20].

NEONATAL PRIMARY CUTANEOUS ASPERGILLOSIS

A number of reports have emerged, predominantly in the last 10 years, of cutaneous aspergillus infection in neonates [49–61]. At least 80% of these infections have been in premature infants, with gestational ages from 24 to 32 weeks at the time of birth, and birthweights of 440–1500 g. The infection occurs in the first month of life.

Premature infants are known to have functional impairment of neutrophils and monocytes, despite normal number of these cells [62]. Additionally, many premature ventilated neonates are receiving systemic corticosteroids. At least eight

of the 18 cases reported thus far have received systemic corticosteroids. Finally, the skin barrier of premature infants is inadequate because of their immaturity, and is subject to trauma from intravenous catheter insertion, tape removal, arm boards and pulse oximeters.

The skin lesions of neonatal premature cutaneous aspergillosis typically begin as an erythematous patch or plaque that develops pustules and eventually ulcerates to form a necrotic eschar [49]. The initial erythematous plaque may be mistaken for an early bedsore, or even an incarcerated inguinal hernia [49]. By definition, primary cutaneous aspergillosis is confined to the skin, without infection in other organs. However, without prompt diagnosis and treatment, systemic infection may follow. Most cases have been as a result of *A. fumigatus* or *A. flavus* infection.

CUTANEOUS INFECTION DUE TO ASPERGILLUS USTUS

A. ustus is a rarely described *Aspergillus* species. However, a number of recent reports have documented human infection with this fungus [63–70]. On malt extract agar, *A. ustus* colonies are dense, cottony, brownish grey, white at the periphery, with a yellow diffusing pigment. Colonial features on potato dextrose agar are similar but a typical brownish exudate may be produced. The microscopic appearance is of smooth, brown, thick-walled conidiophores up to 250 µm long by 5 µm wide, with biserial conidial heads composed of metulae up to 6 µm long by 4 µm wide, and phialides up to 6 µm long by 3.5 µm wide. The conidia are globose, 4–5 µm in diameter, and brown with very rough walls. Irregularly elongated, slightly curved or twisted Hülle cells are often profusely produced in all media.

Previously reported infections with *A. ustus* have been almost exclusively of the lungs or skin. Cutaneous infections have been in patients immunosuppressed by use of systemic corticosteroids or by transplant immunosuppression [63,64,68]. In one reported case, the infection commenced in an area of the skin traumatized after a fall [64]. Interestingly, terbinafine has been the most active agent *in vitro* against these strains [64,65]. In one of only two cases which have been successfully treated, the patient received therapy with topical terbinafine [68].

PROSTHETIC VASCULAR GRAFT INFECTION BY *ASPERGILLUS* IN IMMUNOCOMPETENT PATIENTS

Bacterial infection of vascular prosthetic grafts is a serious event but occurs in less than 3% of patients with grafts in place. Fungal infections of vascular grafts are even less frequent; fewer than 20 cases of prosthetic vascular graft infection by *Aspergillus* spp. have thus far been reported [10–12,71–80]. Interestingly, all of the patients have been immunocompetent, raising suspicions that the grafts were contaminated at the time of surgery. Presumably this is by contamination of the graft in the operating room with airborne fungal spores.

The majority of infections have been either at the thoracic or abdominal aorta. The median time from placement of the graft to diagnosis has been 8 months. Not all patients have presented with fever but most patients had elevated white blood cell counts and erythrocyte sedimentation rates. Four reported cases have had coexisting vertebral osteomyelitis.

Medical therapy, alone, is unlikely to cure the infection. Resection of the infected graft and placement of an extra-anatomic bypass through a clean field appears to be the key to a successful outcome [72].

ASPERGILLUS ENDOCARDITIS IN SOLID-ORGAN TRANSPLANT RECIPIENTS

Fungi are an important cause of endocarditis in solid-organ transplant recipients [81]. Fewer than 20 cases have been reported in published literature as being the result of *Aspergillus* spp. infection, but a number of common characteristics have emerged [81–89]. Liver, lung, heart and kidney transplant recipients with aspergillus endocarditis have been described.

There appears to be a bimodal distribution in terms of time from transplantation to development of endocarditis. One subgroup of patients comprises those with an extremely stormy early post-transplant course with poor function of the transplant organ and renal failure. These patients develop disseminated aspergillosis, including endocarditis, and die within 30 days of transplantation. Endocarditis is not suspected prior to death but is discovered at autopsy. Characteristi-

cally, these patients have infection of the mural endocardium rather than of the valvular endocardium.

A second, and somewhat smaller, subgroup comprises patients who manage to leave hospital but who develop aspergillus endocarditis in the second year after transplantation. These patients may have received augmented immunosuppression for treatment of rejection or may have a history of recent cytomegalovirus infection (which also contributes to immunosuppression) [86,88]. At least two such patients have presented with peripheral embolic phenomena [87,88]. These patients also presented evidence of arterial occlusion, one presenting with a painful, pulseless arm, the other with acute renal failure associated with thrombosis of the renal arteries. In both cases a surgically excised thrombus grew *A. fumigatus*. Despite treatment, all of these patients have died.

It should be noted that, unlike infective endocarditis caused by other organisms, aspergillus endocarditis is exceedingly rarely associated with positive blood cultures. Transthoracic echocardiography may not detect some cases of aspergillus endocarditis visualised by transoesophageal echocardiography [88].

Treatment of previously documented cases of aspergillus endocarditis suspected during life has comprised conventional amphotericin or a lipid preparation of amphotericin. Given recent data showing the superiority of voriconazole over amphotericin for invasive aspergillosis [90], voriconazole may be considered the drug of choice for aspergillus endocarditis. However, there are a number of caveats to this statement. Although immunosuppression should be reduced as much as possible during treatment of invasive aspergillosis, voriconazole may significantly inhibit the metabolism of cyclosporine or tacrolimus. Additionally, many patients who develop invasive aspergillosis post-transplant will have renal failure, yet intravenous voriconazole is not recommended when creatinine clearance falls below 50 mL/min because accumulation of the intravenous vehicle, sulphobutyl ether β -cyclodextrin sodium, occurs in renal failure. At the present time, the role of a combination of voriconazole with amphotericin or caspofungin is uncertain, but animal data [91] would suggest that this combination may provide additional benefits. It is also recommended that patients with aspergillus endocarditis be considered potential candidates

for valve replacement surgery. Unfortunately patients with disseminated aspergillosis rarely have the general physiology capable of withstanding such an operation.

It should be noted that a number of less common molds have been observed to cause endocarditis in transplant recipients. These may initially be mistaken for aspergillus infection. Examples include *Phaeoacremonium parasiticum* in a liver transplant recipient [92], *Fusarium solani* in a lung transplant recipient [93], *Cunninghamella bertholletiae* in a kidney transplant recipient [94] and *Pseudallescheria boydii* in a liver transplant recipient [95]. Like aspergillus endocarditis, the infection is disseminated and almost universally fatal. Each of these cases has occurred in the first 4 months post-transplant and has involved right-sided valves.

UNUSUAL RESPIRATORY MANIFESTATIONS OF INFECTION WITH *ASPERGILLUS* SPP.

In settings other than transplantation or neutropenia, patients with invasive pulmonary aspergillosis may present with symptoms progressing over several weeks to months [96–100]. This chronic form of invasive pulmonary aspergillosis is considerably less common than the acute invasive form. Patients may lack immunocompromise or may have received corticosteroids for chronic pulmonary diseases such as sarcoidosis, may be alcoholic or have diabetes mellitus, chronic granulomatous disease, or human immunodeficiency virus (HIV) infection. The usual symptoms are chronic productive cough, low-grade fever, occasional haemoptysis, malaise and weight loss. Radiologically, cavitation of an area of consolidated lung is usual. The finding of *Aspergillus* in sputum is suggestive, but smokers may have colonisation in the absence of invasive disease. Diagnosis therefore usually requires biopsy evidence of invasive aspergillus hyphae in lung tissue. However, hyphae are often scant. Granulomata are typical; sometimes the process is described histologically as an angioinvasive necrotizing granulomatous pneumonia.

One histologic appearance of chronic pulmonary aspergillosis is bronchocentric granulomatosis [101–103]. About 50% of patients have asthma. Hence, bronchocentric granulomatosis is regarded by some as more akin to a localised allergic

bronchopulmonary aspergillosis than to a true invasive process. Patients usually have chronic symptoms such as cough, low-grade fever, malaise, dull chest pain and haemoptysis. Radiologically, a focal upper lobe lesion is usually seen.

Aspergillus tracheobronchitis is seen characteristically in lung transplant recipients, although it has also been observed rather commonly in HIV-infected and immunocompetent patients [104–107]. Rare cases have been reported in other groups, such as bone marrow transplant recipients. In lung transplant recipients the disease usually occurs in the first month post-transplant. Tracheobronchitis is observed on routine bronchoscopy, centered around the suture line. Patients are generally asymptomatic or have symptoms attributable to the transplant, with chest radiographs unchanged from baseline. However, as the disease progresses, symptoms become more pronounced with a monophonic wheeze becoming particularly prominent.

Bronchoscopically, the appearance is of severe tracheobronchitis progressing to multiple ulcers at the site of anastomosis. Sequelae include acute invasive pulmonary aspergillosis, severe bronchial stenosis, anastomotic dehiscence and bronchial necrosis with bronchoarterial fistula formation. Some patients develop extensive pseudomembranes, which can completely occlude the lumen of large airways. Such patients are extremely difficult to ventilate, and may die of respiratory insufficiency.

Bronchial stump aspergillosis is a rare and unusual sequel of lung resection, first described in Japan [108,109]. Typically, 6–12 months after lung resection (during which silk sutures were used), the patient develops productive cough and haemoptysis. The sputum may be foul smelling and contain fungal material or silk-suture material. The cause is secondary colonisation of the suture material which is protruding into the bronchial lumen. Local inflammation and then necrosis of the bronchial mucosa result. Chest radiography is usually unchanged compared to baseline.

CONCLUSIONS

Invasive aspergillosis has a myriad of clinical presentations. It has been known for many years that in disseminated aspergillosis the fungus can be grown from a huge variety of organs. How-

ever, a current clinical challenge is the early detection of invasive aspergillosis isolated to unusual sites, sometimes even in immunocompetent individuals. The combination of early diagnosis, appropriate treatment with new antifungal options such as voriconazole, and careful consideration of adjunctive surgical therapy should improve the outcome of such patients.

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