Management of pulmonary aspergillosis in AIDS: an emerging clinical problem

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Abstract

Aims—To review the clinical, radiographic, and therapeutic features of 11 cases of respiratory *Aspergillus* infection in patients with AIDS.

Methods—All induced sputum and bronchoalveolar lavage samples obtained from HIV seropositive patients between January 1985 and March 1993 were analysed for *Aspergillus* species. Additionally, where appropriate, bronchial or renal biopsy specimens, or both, were taken before treatment had started.

Results—In 11 patients *Aspergillus fumigatus* was identified in alveolar samples obtained by sputum induction. This was confirmed by bronchoalveolar lavage in eight. Three patients had *Aspergillus* plaques in the trachea and bronchus, while a fourth patient had an aspergilloma. Risk factors for *Aspergillus* infection were present in all patients, including corticosteroid treatment in three cases and neutropenia in four, three of whom had received chemotherapy for Kaposi's sarcoma. Four patients had concomitant cytomegalovirus infection. Ten patients had a CD4 count of less than 50 cells/mm³ while one patient had a disseminated T cell lymphoma with a CD4 count of 242 cells/mm³. Of the three patients with samples obtained by sputum induction who did not undergo bronchoscopy, two had a normal chest x ray picture and the third had a right lobar pneumonia complicating an aggressive lymphoma. All three were treated with itraconazole 200 mg twice a day without further investigation.

Survival from the time of diagnosis of *Aspergillus* infection was short: seven patients died within six weeks, although only one death was directly attributed to pulmonary aspergillosis. At six monthly follow up, one patient, who initially had a positive *Aspergillus* culture from bronchial washings and a normal chest radiograph, developed a renal aspergilloma despite the disappearance of *Aspergillus* sp from the sputum.

Conclusion—Pulmonary aspergillosis is an important clinical problem in patients with AIDS with a CD4 count of less than 50 cells/mm³. Furthermore, patients with *Aspergillus* sp in sputum induction or

bronchial washings may develop disseminated disease despite adequate treatment of the primary infection.

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Pulmonary aspergillosis is rarely found in HIV seropositive patients compared with its prevalence in other conditions producing a similar degree of immunosuppression, such as organ transplantation, lymphoma, and leukaemia.¹⁻⁵ However, these patients are more likely to have impaired phagocytic function because of drug treatment than patients with AIDS.

Although the diagnosis of pulmonary aspergillosis is initially suggested by a positive sputum culture, in immunocompetent people the presence of a few colonies of *Aspergillus* present on artificial culture media may only indicate harmless colonisation or contamination. In immunosuppressed patients the finding of *Aspergillus* in sputum may be more important, particularly when the growth is heavy and when the patient is neutropenic.⁶

Aspergillus may colonise the upper respiratory tract without causing disease, or it can cause a wide spectrum of clinical illness. This may be limited to the bronchi, with or without macroscopic plaques, or may be associated with local invasion of the lung, producing radiographic changes or with widespread dissemination of infection.^{2,6}

Even though we have routinely cultured bronchoalveolar lavage and sputum induction specimens for fungi since 1985, we have only regularly detected *Aspergillus* in such specimens since 1992. We review the findings and clinical course of these patients.

Methods

Patients found to be HIV antibody positive had their personal details and subsequent clinical course recorded on the departmental computer. By comparing this record with that held within the Department of Mycology, of all patients having sputum induction or bronchoalveolar lavage, a complete collection of those diagnosed with pulmonary aspergillosis was assured.

All patients fasted overnight before bronchoscopy or sputum induction. Contamination of the induced sputum specimen with oral debris was avoided by cleansing of the buccal mucosa, tongue, and gums with a

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Clinical details of patients studied

Case No	AIDS	Neutrophils 10 ⁹ /l	CD4 10 ⁹ /l	Problems and antibiotic treatment	Chest x-ray, PaO ₂ , bronchoscopy	Antifungal treatment	Outcome
1	4-91	0.3	35	Fever, dry cough, breathlessness, Kaposi's sarcoma—treatment vincristine, bleomycin. CMV of oesophagus: azithromycin, septrin.	Widespread infiltrate PO ₂ 11.2 <i>Aspergillus</i> plaques	Itraconazole tablet 400 mg/day (6/52)	Died 6/52: necropsy sepsis, pulmonary aspergillosis
2	5-90	4.0	50	Fever, dry cough. Kaposi's sarcoma—treatment vincristine, bleomycin, prednisolone 40mg. 7-92 <i>Aspergillus</i> and <i>Pseudomonas</i> : teicoplanin, cefuroxime.	Infiltrate Bilateral PO ₂ 12.4 <i>Aspergillus</i> plaques	Itraconazole tablet 400 mg/day (1/52)	Died 1/52: multisystem failure
3	8-88	0.5	30	Fever, dry cough tuberculosis/leishmaniasis, cannabis smoker. 8-89 <i>A. fumigatus</i> : isoniazid, NA-stibogluconate.	Hilar shadowing on right PO ₂ 8.7 No plaques	Itraconazole tablet 400 mg/day (6/52)	Died 12/12: end stage HIV disease
4	4-92	4.0	242	Dry cough, breathlessness, T cell lymphoma of gut, stage 4B, ventilated after laparotomy. 5-92 <i>A. fumigatus</i> : ciprofloxacin, prednisolone.	Left lower lobe infiltrate PO ₂ 9.2 No bronchoscopy	Itraconazole intravenously 400 mg/day (1/52)	Died 1-52
5	4-92	3.8	22	Dry cough, breathlessness, emphysema. 11-92 <i>A. fumigatus</i> : ciprofloxacin.	Hyperinflation PO ₂ 11.2 No plaques	Intraconazole elixir 400 mg/day (2/12)	Well Renal aspergilloma
6	12-92	4.4	48	Fevers, breathlessness, cryptosporidiosis, diarrhoea, ARSC on ERCP. CMV colitis. 1-93 <i>A. fumigatus</i> : foscarnet, amphotericin.	Diffuse infiltrate PO ₂ 7.0 <i>Aspergillus</i> plaques	Amphotericin B 1 mg/kg/day (2/52)	Died 2/52: multisystem failure
7	1-93	4.1	12	Generalised malaise; CMV retinitis and pneumonitis. 1-93 <i>A. fumigatus</i> and <i>Exophiala dermatitidis</i> : dapsone, foscarnet.	Aspergilloma right upper lobe PO ₂ 14.1 No plaques	Itraconazole tablet 400 mg/day 2/12	Well
8	4-92	4.1	18	Fevers, dry cough, breathlessness, CMV/pneumonitis/colitis. 2-93 <i>A. fumigatus</i> : ampicillin, metronidazole, cefuroxime, amphotericin, ganciclovir	Widespread bilateral reticulo/nodular shadowing PO ₂ 8.2 No plaques	Amphotericin B 1 mg/kg/day IV (3/52)	End stage disease: unwell
9	1-92	1.8	4	Fevers, productive cough, breathlessness; microsporidial diarrhoea, ARSC on ERCP—treatment antibiotics. 2-93 <i>A. fumigatus/flavus</i> : ciprofloxacin, co-trimoxazole.	Normal PO ₂ 7.4 No bronchoscopy	Itraconazole elixir 400 mg/day (3/52)	Died 4/52: multisystem failure
10	11-92	0.4	40	Fevers, dry cough. Kaposi's sarcoma—treatment razoxane and radiotherapy. 3-93 <i>A. fumigatus</i> : co-trimoxazole.	Normal PO ₂ 12.5 No bronchoscopy	Itraconazole elixir 400 mg/day (4/52)	Died 4/52: multisystem failure
11	12-93	0.2	1	Fevers, dry cough, breathlessness, Kaposi's sarcoma of skin and lung. Vincristine 1 mg, bleomycin 15mg. 1-93 <i>A. fumigatus</i> : amoxycillin.	Kaposi's sarcoma nodules on lung PO ₂ 13.0 No plaques	Itraconazole tablet 400 mg/day (4/52)	Died 5/52: end stage HIV disease

ARSC = AIDS related sclerosing cholangitis; ERCP = endoscopic retrograde cholangiopancreatogram.

toothbrush and thoroughly rinsing with water. Sputum was obtained by inhalation of 20–30 ml of 3% physiological saline through an ultrasonic nebuliser (De Vilbiss, Feltham, Middlesex). Gentle chest percussion was used when necessary and two sputum specimens were promptly taken to the laboratory. Bronchoalveolar lavage specimens were taken from the right middle lobe bronchus or alternatively the lobe with radiological abnormality. In those patients with abnormal white plaques in the bronchial tree, biopsy specimens were taken for culture and histological assessment to confirm the presence of fungal hyphae.

Standard mycological culture techniques were used to identify *Aspergillus* species. Samples of bronchial lavage and sputum were mixed with an equal volume of Sputasol (Oxoid) for 15 minutes at 37°C with regular mixing, after which the sample was centrifuged at 3000 rpm for 10 minutes. The supernatant fluid was discarded and 25 ml of the deposit was cultured on Sabouraud's dextrose agar plates with and without chloramphenicol for up to eight weeks at 30°C and 37°C. The presence of fungi in the medium was identified using standard KOH/Parker's blue ink solution. All patients had a heavy growth of *Aspergillus fumigatus*. Initial positive induced sputa were confirmed either by subsequent bronchoalveolar lavage or a second induced sputum before inclusion in this report.

Figure 1(A) (B) White raised plaques seen in trachea mainstem and segmental bronchi. This appearance is highly suggestive of tracheo-bronchial aspergillosis which can be confirmed by brushings and biopsy.

Figure 2 Pulmonary aspergilloma. (A) Pre-treatment radiograph: aspergilloma; right upper zone consolidation. (B) Post-treatment radiograph; partial resolution of aspergilloma. (C) Radiograph showing recurrence of pulmonary aspergilloma, two months after stopping antifungal treatment. Left mid-zone consolidation has developed.

Results (table)

Between May 1992 and March 1993 *Aspergillus* sp were cultured from 10 of a total of 536 sputum induction samples and eight of 182 bronchoalveolar lavage samples obtained from HIV seropositive patients with respiratory symptoms. By contrast, between January 1985 and April 1992, only one sputum sample was positive for *Aspergillus* from a total of 1270 samples analysed (case 3).

Patients underwent sputum induction because of non-specific symptoms of non-productive cough, breathlessness, and fever, with hypoxia being present in half the cases (table). Two patients had a normal chest x ray picture and a further patient had only hyper-inflated lung fields at presentation. The other patients had diffuse infiltration of the lungs and one patient had a cavitating aspergilloma (table).

Pulmonary aspergillosis was only found in those with advanced HIV infection after AIDS had been diagnosed (median seven months, range one to 26 months). The CD4 count was less than 50 mm^{-3} in 10 patients at the time of diagnosis. In the eleventh patient the CD4 count was 242 mm^{-3} , although lymphoma had recently been diagnosed.

Neutropenia (neutrophil count of 0.5×10^9 per litre or less) was a likely contributing factor in four of 11 patients and was associated with chemotherapy for Kaposi's sarcoma in three. Broad spectrum antibiotics were prescribed in eight patients, three of whom were neutropenic. Four patients had cytomegalovirus affecting the colon, lung, or oesophagus. One patient was known to have smoked marijuana regularly (table).

Bronchoscopy was not performed in two of the three who had a normal chest x ray picture and who were not clinically seriously ill nor in a third terminally ill patient with high grade lymphoma (case 4). Bronchoscopy in the other eight patients who had an abnormal chest x ray picture revealed tracheobronchial *Aspergillus* plaques in three (fig 1). A heavy growth of *Aspergillus* was obtained from bronchoalveolar lavage specimens in all eight cases.

All patients were treated with antifungal drugs, two with amphotericin B and nine with itraconazole. In only one of the seven patients who died within six weeks was *Aspergillus* not eradicated from the sputum samples, although in this patient tracheobronchial *Aspergillus* plaques substantially regressed after three weeks of intravenous itraconazole. At the time of writing, two patients have survived for more than one year, one with negative sputum cultures for *Aspergillus*. One initially presented with an aspergilloma of the lung (fig 2) and a second patient (case 5) without bronchoscopic evidence of *Aspergillus* plaques developed a renal aspergilloma after six months of follow up (fig 3).

Death in eight of the 11 patients was expected because of complications of advanced HIV disease and one necropsy confirmed the presence of widespread sepsis and extensive pulmonary aspergillosis.

Figure 3 Renal biopsy specimen. Area of necrosis showing aspergillus hyphae with septations, vesicular swellings, and dichotomous branchings (periodic acid-Schiff).

Discussion

Aspergillus is a ubiquitous fungal organism of which several hundred species are known to exist, although only a few cause disease in people. The most commonly encountered species is *Aspergillus fumigatus*. The portal of entry for infection is predominantly the respiratory tract where *Aspergillus* may colonise the bronchi or lung cavities, particularly where parenchymal damage has been caused by previous infections.

No case of pulmonary aspergillosis in AIDS has been reported in Britain, but reports are now being published elsewhere.^{1,2,7,8} In a number the diagnosis has been made at post mortem examination.⁹ Disseminated disease affecting the heart,¹⁰ central nervous system¹¹ and pancreas¹² has also been reported in patients with AIDS. *Candida* species have been cultured from 10% of sputum samples taken from HIV seropositive patients in our unit over the past seven years, while *Aspergillus* species were only cultured in 11, 10 in the past 12 months. The temporal clustering of these patients and the finding of a heavy growth of *Aspergillus* repeatedly in these patients implies that these organisms are an important pathogen. This was confirmed in three cases with tracheobronchial plaques and in a fourth patient with a lung aspergilloma. A further patient with *Aspergillus* in his sputum on presentation, with a normal chest x ray picture and no *Aspergillus* plaques at bronchoscopy, developed a renal aspergilloma six months later. A recent study by Denning and colleagues showed a similar incidence of tracheobronchial plaques in 12 patients with pulmonary aspergillosis, two of whom had widely disseminated disease. A French cooperative study has reported 33 cases of pulmonary aspergillosis from 17 centres. They found that 91% of the cases were reported during the preceding three years and suggested that *Aspergillus* infection is an emerging complica-

tion in patients with AIDS.¹ Our experience confirms this.

The factors which predispose to an increased risk of aspergillosis remain controversial. Both neutropenia and administration of steroids are accepted risk factors and were present in some of our patients.^{13,14} It has also been suggested that smoking marijuana increases the risk of inhaling spores and one of our patients was a regular user.^{2,15} It is not clear how important the concurrent use of broad spectrum antibiotics in eight patients and the presence of cytomegalovirus infection in four may have been.¹⁶ Many patients with advanced AIDS require broad spectrum antibiotics and at least a third would be expected to develop cytomegalovirus infection. The most likely reason for the recent increase in frequency of *Aspergillus* infection in patients with AIDS in our unit is that patients are surviving longer with more severe immunosuppression.

The treatment of pulmonary aspergillosis in AIDS is complicated both because of the uncertainty that this fungus is a pathogen in all cases and because patients are often seriously ill with multisystem failure at presentation. Although amphotericin B is probably the most effective agent, it is extremely toxic to the kidneys and must be given intravenously.^{1,2} It would be preferable to have an oral agent and itraconazole is active against *Aspergillus* in vitro. Its clinical effectiveness is unclear, perhaps because of the poor absorption of the drug which has been reported to occur in HIV seropositive patients.^{17,18} This may be improved using itraconazole solution (Abstract presented at the International Congress of Antimicrobial Agents and Chemotherapy, Anaheim, California, 1992). Further advances in our understanding of how best to treat such patients will require multicentre studies of itraconazole, amphotericin B, and newer antifungal agents.

The clinical relevance of finding *Aspergillus* in the sputum of a non-HIV infected person with a normal chest x ray picture depends on the clinical setting, particularly the presence of neutropenia.⁶ In the context of HIV seropositive patients, *Aspergillus* in the sputum in two successive samples requires further evaluation, which should include bronchoscopy. We feel that early treatment with amphotericin B or itraconazole should be considered, even in those with a normal bronchoscopy, as this may prevent dissemination.

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