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. Inhalation of Aspergillus sp, bronchial washings may develop disseminated disease despite adequate treatment of the primary infection.

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. 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. 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.

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
<table>
<thead>
<tr>
<th>Case No</th>
<th>AIDS</th>
<th>Neutrophils 10^9/l</th>
<th>CD4 10^9/l</th>
<th>Problems and antibiotic treatment</th>
<th>Chest x-ray, PaO₂, bronchoscopy</th>
<th>Antifungal treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-91</td>
<td>0-3</td>
<td>35</td>
<td>Fever, dry cough, breathlessness, Kaposis's sarcoma—treatment vincristine, bleomycin. CMV of oesophagus: aspergillus, sepsis.</td>
<td>Widespread infiltrate PO, 12 Aspergillus plaques</td>
<td>Itraconazole tablet 400 mg/day (6/52)</td>
<td>Died 6/52: necropsy sepsis, pulmonary aspergillosis</td>
</tr>
<tr>
<td>2</td>
<td>5-90</td>
<td>4-0</td>
<td>50</td>
<td>Fever, dry cough. Kaposis's sarcoma—treatment vincristine, bleomycin, prednisilone 40mg, 7-92 Aspergillus and Pseudomonas: teicoplanin, cefuroxime.</td>
<td>Infiltrate Bilateral PO, 12-4 Aspergillus plaques</td>
<td>Itraconazole tablet 400 mg/day (1/52)</td>
<td>Died 1/52: multisystem failure</td>
</tr>
<tr>
<td>3</td>
<td>8-88</td>
<td>0-5</td>
<td>30</td>
<td>Fever, dry cough tuberculosis/leishmaniasis, cannabis smoker. 9-89 A fumigatus: ioniazid, NA-stibogluconate.</td>
<td>Hilar shadowing on right PO, 8-7 No plaques</td>
<td>Itraconazole tablet 400 mg/day (6/52)</td>
<td>Died 12/12: end stage HIV disease</td>
</tr>
<tr>
<td>4</td>
<td>4-92</td>
<td>4-0</td>
<td>242</td>
<td>Dry cough, breathlessness, T cell lymphoma of gut, stage 4B, vented after laparotomy. 5-92 A fumigatus: ciprofloxacin, prednisilone.</td>
<td>Left lower lobe infiltrate PO, 9-2 No bronchoscopy Hyperinfiltration PO, 11-2 No plaques</td>
<td>Itraconazole intravenously 400 mg/day (1/52)</td>
<td>Died 1/52</td>
</tr>
<tr>
<td>5</td>
<td>4-92</td>
<td>3-8</td>
<td>22</td>
<td>Dry cough, breathlessness, emphysema. 11-92 A fumigatus: ciproflloxacin.</td>
<td>No plaques</td>
<td>Intraconazole elixir 400 mg/day (2/12)</td>
<td>Well</td>
</tr>
<tr>
<td>6</td>
<td>12-92</td>
<td>4-4</td>
<td>48</td>
<td>Fevers, breathlessness, cryptococcosis, diarthrea, ARSC on ERCP. CMV colitis. 1-93 A fumigatus: fosarnet, amphotericin.</td>
<td>Diffuse infiltrate PO, 7-0 Aspergillus plaques</td>
<td>Amphotericin B 1 mg/kg/day (2/52)</td>
<td>Died 2/52: multisystem failure</td>
</tr>
<tr>
<td>7</td>
<td>1-93</td>
<td>4-1</td>
<td>12</td>
<td>Generalised malaise; CMV retinitis and pneumonitis. 1-93 A fumigatus and Exophiala dermatisides: dapson, foscarnet.</td>
<td>No plaques</td>
<td>Itraconazole tablet 400 mg/day 2/12</td>
<td>Well</td>
</tr>
<tr>
<td>8</td>
<td>4-92</td>
<td>4-1</td>
<td>18</td>
<td>Fevers, dry cough, breathlessness, CMV/ pneumonitis/colitis. 2-93 A fumigatus: ampicillin, metronidazole, cefuroxime, amphotericin, ganciclovir.</td>
<td>Widespread bilateral reticulo/ nodular shadowing PO, 8-2 No plaques</td>
<td>Amphotericin B 1 mg/kg/day IV (3/52)</td>
<td>End stage disease: unwell</td>
</tr>
<tr>
<td>9</td>
<td>1-92</td>
<td>1-8</td>
<td>4</td>
<td>Fever, productive cough, breathlessness, microsporidial diarthrea, ARSC on ERCP—treatment antibiotics. 2-93 A fumigatus/flavus: ciprofloxacin, co-trimoxazole.</td>
<td>Normal PO, 7-4 No bronchoscopy</td>
<td>Itraconazole elixir 400 mg/day (3/52)</td>
<td>Died 4/52: multisystem failure</td>
</tr>
<tr>
<td>11</td>
<td>12-93</td>
<td>0-2</td>
<td>1</td>
<td>Fevers, dry cough, breathlessness, Kaposis's sarcoma of skin and lungs. Vincristine 1 mg, bleomycin 15mg. 1-93 A fumigatus: amoxycillin.</td>
<td>No plaques</td>
<td>Itraconazole tablet 400 mg/day (4/52)</td>
<td>Died 5/52: end stage HIV disease</td>
</tr>
</tbody>
</table>

ARSC = AIDS related scleroderma; 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 spura 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.](http://jcp.bmj.com/)

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Figure 2 Pulmonary aspergillosa. (A) Pre-treatment radiograph: aspergillosa; right upper zone consolidation. (B) Post-treatment radiograph: partial resolution of aspergillosa. (C) Radiograph showing recurrence of pulmonary aspergillosa, 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 aspergillosa (table).

Pulmonary aspergillosa 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 eleven patient the CD4 count was 242 mm⁻³, although lymphoma had recently been diagnosed.

Neutropenia (neutrophil count of 0.5 x 10⁹ 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 aspergillosa of the lung (fig 2) and a second patient (case 5) without bronchoscopic evidence of Aspergillus plaques developed a renal aspergillosa 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 aspergillosa.
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.\(^1\) In a number of previous cases diagnosis has been made at post mortem examination.\(^9\) Disseminated disease affecting the heart,\(^10\) central nervous system\(^1\) and pancreas\(^11\) 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 complic-
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