Pulmonary Aspergillosis in Immunosuppressed Patients with Haematological Malignancies

R. L. SPEARING, D. H. PAMPHILON and A. G. PRENTICE

From the Department of Haematology, Derriford Hospital, Plymouth PL6 8DH

Accepted 2 February 1986

SUMMARY

Invasive pulmonary aspergillosis as a cause of mortality and morbidity in patients with haematological malignancies is becoming more common. Predisposing factors are powerful immunosuppressive chemotherapy, neutropenia and synergistic combinations of antibiotics of great potency and wide spectrum of activity. Clinical and radiological signs are heterogeneous, sometimes misleading and often absent. Treatment is often empirical on suspicion alone. Amphotericin B is the only effective drug but it has marked toxicity, mainly renal. Infection is usually fatal without adequate treatment. This paper describes eight cases of invasive pulmonary aspergillosis seen in one centre in two years, reviews the literature and assesses associated problems.

INTRODUCTION

Increasing success in the treatment of acute leukaemia and lymphomas in the past 20 years has been due to increased intensity of chemotherapy and improved ability to support patients who are thrombocytopenic, neutropenic and immunosuppressed for long periods. However, infection still accounts for 70 per cent of deaths in patients with acute leukaemia [1], and patients undergoing intensive remission induction have a mean of at least two septicaemias [2]. Isolation of pathogens during febrile episodes in these patients is very variable, as low as 32 per cent in one recent study [3]. The majority of identifiable organisms are Gram-negative bacilli and Gram-positive cocci but aspergillus is now increasingly recognised [4]. The true frequency of aspergillosis as a cause of fever in these patients is controversial. We present our recent experience of pulmonary aspergillosis in acute leukaemia and discuss the current controversies and problems in management.

CASE REPORTS

Case 1

A 37-year-old woman presented with acute monoblastic leukaemia. Remission was achieved with standard chemotherapy (daunorubicin, cytosine arabinoside and thioguanine) but six
months later she relapsed. Further intensive chemotherapy (amsacrine and etoposide) failed to achieve a second remission. She was pancytopenic with a neutrophil count of less than $0.5 \times 10^9/l$ intermittently for long periods. After a further five months she developed fever which responded temporarily to intravenous piperacillin and gentamicin. Neutrophil count remained less than $0.5 \times 10^9/l$. Her previously normal chest radiograph showed consolidation in the right lower lobe which spread rapidly to the left lung field with development of cystic areas (Fig. 1). Nine days later she died of cardiac tamponade.

Post-mortem examination of the lungs revealed several discrete infiltrative masses. Microscopic examination showed the classical argyrophilic branching hyphae of aspergillus. Serum precipitins to aspergillus were not identified.

**Case 2**

A 16-year-old girl presented with acute lymphoblastic leukaemia. An initial fever with widespread shadowing on chest radiograph responded to intravenous piperacillin and gen-

![FIG. 1. Case 1: right lower lobe consolidation with cystic areas in the left lung.](image-url)
tamicin. No pathogen was identified. She was started on daunorubicin, vincristine, prednisolone and asparaginase, but after two weeks she again developed fever and complained of mild non-productive cough and right-sided pleuritic chest pain. *Staphylococcus epidermidis* and *Streptococcus sanguis* were grown from several consecutive blood cultures. Despite intravenous gentamicin and cefotaxime, respiratory symptoms rapidly increased over the next four days when her chest radiograph showed widespread shadowing over the right lung field (Fig. 2) and she required ventilation. Intravenous amphotericin B (0.6 mg/kg/day) was started empirically but she developed increasing consolidation of both lung fields and died three days later. During life no hyphae or pathogens were isolated from the sputum and serum fungal precipitins were not found. Post-mortem examination showed widespread pulmonary infiltration by *Aspergillus fumigatus*.

**Case 3**

A 71-year-old woman presented with pancytopenia (neutrophil count less than $0.1 \times 10^9/\text{l}$), due to relapse of acute myelomonoblastic leukaemia two years after initial chemotherapy.
FIG. 3. (a) Case 3: wedge shaped segmental consolidation of right upper lobe. (b) Case 3: mycetoma with resolution of surrounding consolidation.
Pulmonary Aspergillosis in Haematological Malignancy

A further course of chemotherapy was given (daunorubicin and cytosine arabinoside) but failed to induce a second remission. One week after successful treatment of a left tonsillar abscess with intravenous piperacillin and gentamicin, she developed fever; again radiological examination showed a wedge-shaped consolidation in the right upper lobe (Fig. 3(a)) without abnormal physical signs. The chest radiograph was unchanged after six days of intravenous piperacillin and gentamicin, and amphotericin B (0.6 mg/kg/day) was added. Within 48 h fever had resolved. Radiological signs of a mycetoma then developed with resolution of most of the surrounding pneumonic changes (Fig. 3(b)). There was no sputum and serum fungal precipitins were not found. Two weeks later she developed uncontrolled atrial fibrillation and died with a mesenteric embolus. There was no autopsy.

Case 4
A 53-year-old female presented with a diagnosis of acute myeloid leukaemia and a neutrophil count of less than $0.1 \times 10^9/l$. Initial chemotherapy (daunorubicin and cytosine arabinoside) was
interrupted twice by fever but settled with intravenous piperacillin and gentamicin. Following remission induction she developed a further low-grade pyrexia but was otherwise well with no abnormal physical signs. Chest radiograph revealed an opacity in the right upper lobe which tomography showed to be a solid mass (Fig. 4). Fungal hyphae were not seen in sputum and serum fungal precipitins were not found. No other organisms were isolated.

Amphotericin B was started and continued at 0.6 mg/kg per day for one month and then in the same dose twice weekly for a further two weeks. There was complete resolution of the mass. A further consolidation course of chemotherapy was given concurrently with amphotericin B.

**Case 5**

A 58-year-old housewife presented with acute monoblastic leukaemia. Complete remission was induced with standard chemotherapy (daunorubicin and cytosine arabinoside) over the next six weeks. During that time she was neutropenic and had two episodes of pyrexia which resolved with piperacillin, tobramycin and metronidazole. No pathogens were identified. She remained well on maintenance chemotherapy until relapse of her leukaemia six months later. Re-induction of remission was attempted with amsacrine and etoposide but malignant blast cells persisted in a hypoplastic marrow after eight weeks. She was neutropenic (<0.5 × 10⁹/l) for a total of seven weeks.

Four days after the second course of chemotherapy, she complained of pleuritic left-sided chest pain and dyspnoea. Temperature was 39°C and there was widespread consolidation in both lung fields (Table I, Fig. 5(a)).

Invasive pulmonary aspergillosis was suspected despite absence of hyphae in sputum and negative serum fungal precipitins and she was given intravenous amphotericin B (0.6 mg/kg/day), piperacillin and gentamicin. Fever persisted for three days but there was rapid improvement in symptoms. On the eighth day tomography demonstrated the solid and infiltrative nature of the lesion in the right-upper lobe (Fig. 5(b)).

There was slow improvement in chest symptoms and signs and by day 14 there was considerable resolution of the radiological consolidation but cavitation had appeared in the right-upper and left-lower lobes. Thereafter there was a steady increase in consolidation throughout these lobes despite daily amphotericin B. Twenty-eight days after the onset of pleuritic pain the leukaemia was still in relapse and the patient requested that all treatment should cease. She died within five days and autopsy was not performed.

**Case 6**

A 54-year-old housewife presented with pancytopenia due to acute myeloblastic leukaemia. Two courses of standard chemotherapy were given to induce remission. Fever developed after the first course. *E. coli* was isolated from blood cultures but fever persisted over the next three weeks, despite the continued administration of broad-spectrum antibiotics. At this stage amphotericin B was added. Following the first dose of amphotericin (0.25 mg/kg given over six hours) she developed ventricular fibrillation. She had only received a total of 240 mg/m² of anthracyclines and electrolytes were normal.

Over the next 48 h radiologcal evidence of patchy bilateral consolidation developed and antibiotics and amphotericin B were continued, but the latter was stopped when acute renal failure developed. The patchy pulmonary shadowing became worse and the patient could not be ventilated. She died seven weeks after admission. The neutrophil count had been less than 0.5 × 10⁹/l from the time of admission until one week before death when haematopoietic recovery was apparent. Autopsy confirmed consolidating bronchopulmonary aspergillosis. There was no evidence of myocardial infarction and bone marrow was normal.
<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Initial diagnosis</th>
<th>Time from initial diagnosis to developing invasive pulmonary aspergillosis (months)</th>
<th>Broad spectrum synergistic antibiotics in preceding month</th>
<th>Recent steroid treatment</th>
<th>Other recent cytotoxic chemotherapy</th>
<th>Neutropenia (&lt;0.5 × 10⁹/l)</th>
<th>Symptoms other than PUO</th>
<th>Abnormal physical signs in chest</th>
<th>Initial radiological changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>F</td>
<td>Acute monocytic leukaemia</td>
<td>11</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Partial single lobe consolidation</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>Null cell acute lymphoblastic leukaemia</td>
<td>0.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Dry cough and pleuritic chest pain</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>F</td>
<td>Acute myelomonocytic leukaemia</td>
<td>24</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Wedge shaped consolidation in single lobe</td>
</tr>
<tr>
<td>53</td>
<td>F</td>
<td>Acute myelocytic leukaemia</td>
<td>1</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Solid infiltrating mass in single lobe</td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>Acute monocytic leukaemia</td>
<td>10</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>Dyspnoea and pleuritic chest pain</td>
<td>Consolidation in R. upper and L. lower lobes</td>
<td>Consolidation in R. upper and lower lobes and lingula</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>F</td>
<td>Acute myelocytic leukaemia</td>
<td>1.5</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Patchy bilateral bronchopneumonic consolidation</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>Acute myelocytic leukaemia</td>
<td>&lt;0.5</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>Consolidation in R. mid-zone</td>
<td>Consolidation in R. middle and lower lobes and in left mid-zone</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>Hodgkin's disease</td>
<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Dry cough and pleuritic chest pain</td>
<td>0</td>
<td>Consolidation in R. upper and lower lobes and left mid-zone</td>
<td></td>
</tr>
</tbody>
</table>
FIG. 5(a). Case 5: right upper lobe, right lower lobe, left lower lobe and lingular consolidation before treatment.

Case 7

A 70-year-old male presented with acute myeloblastic leukaemia transforming from idiopathic myelofibrosis. Remission was attempted with standard chemotherapy (daunorubicin and cytosine arabinoside). He was neutropenic from the start of chemotherapy and nine days later he developed fever with no clinical or radiological signs of localised infection. The fever did not respond to intravenous piperacillin and gentamicin and on the fifth day consolidation developed in the right middle and lower lobes and left mid-zone. Invasive pulmonary aspergillosis was suspected and intravenous amphotericin B (0.6 mg/kg/day) was added. He remained pyrexial with unchanged clinical signs, but radiological changes became worse until he died 10 days later. At autopsy he had diffuse invasive pulmonary aspergillosis most marked in the areas first seen on the chest radiograph. A Klebsiella sensitive to piperacillin and
gentamicin was grown from post-mortem sputum but aspergillosis was confirmed histologically as the major cause of the pneumonia.

Case 8
A 33-year-old male was admitted 10 days after successful completion of six months of combination chemotherapy for relapsed Hodgkin's disease with a dry cough, right-sided pleuritic chest
FIG. 6. (a) *Case 8*: right middle lobe, right lower lobe and left mid-zone consolidation. (b) *Case 8*: tomogram of whole chest showing cavitation in right lobe consolidation.
pain, fever of 39°C and neutropenia (<0.5×10⁹/l). There were no abnormal chest signs but the chest radiograph showed consolidation in the right lower lobe and the left mid-zone (Fig. 6(a)). Blood cultures were sterile and there was no sputum. A diagnosis of bacterial pneumonia was made and broad-spectrum antibiotics (cefotaxime and gentamicin) were given intravenously. The neutrophil count returned to normal within five days and he began to produce copious purulent sputum from which no organisms were cultured and in which no hyphae were seen. The fever was persistent and progression of radiological abnormalities with cavitation in some areas was shown on the whole chest tomogram (Fig. 6(b)). Sputum, nasal swab and blood cultures remained sterile and hyphae were repeatedly absent. Fungal precipitins were not found. A lung scan showed matched ventilation and perfusion, excluding pulmonary embolism and infarction. The C-reactive protein level in the serum was persistently high.

Invasive pulmonary aspergillosis was suspected and intravenous amphotericin B was given. There was a rapid response with lysis of fever in two days, clearing of sputum, and improved well being. A total of 910 mg of amphotericin B was given over seven weeks, with slow but complete resolution of the radiological signs.

DISCUSSION

Aspergillosis is a significant cause of death in patients with haematological malignancies [4]. Post-mortem studies show a marked rise in the incidence over the last two decades [5, 6] and it is now the most common invasive fungal infection affecting the lung in this group of patients [7, 8]. This rise may be due to the increase in intensity and duration of treatment of these tumours. The incidence varies considerably but in some series as many as 15 to 40 per cent of patients who die of acute leukaemia have evidence of aspergillosis [6, 7].

The lung is the most common site of infection, being affected in more than 90 per cent of cases in most series [9, 10], with the gastrointestinal tract and central nervous system being the next most common sites of infection. In the immunocompetent patient aspergillus infection presents either as allergic bronchopulmonary aspergillosis or as an aspergilloma in a pre-existing lung cavity without tissue invasion. Aspergillomata are often asymptomatic for long periods in immunocompetent patients. In contrast, the hallmark in the immunocompromised patient is rapidly spreading tissue invasion, associated with a fulminant clinical course which is uniformly fatal if not treated aggressively. Only rarely does the invasive form of the disease occur in patients who are not immunocompromised [11, 12]. The two most common pathological forms seen in the immunocompromised patient are a necrotising bronchopneumonia and haemorrhagic pulmonary infarction.

Risk factors have been stated to be recent broad-spectrum antibiotics, steroids and neutropenia [6, 10]. However only the last has been shown to occur more frequently in patients developing aspergillosis than in other immunocompromised patients, the incidence increasing with the duration of the neutropenia [13]. The mechanism by which antibiotics predispose to aspergillosis is probably by sterilisation of the respiratory tract; in one study 14 of 61 patients with sterile nasal cultures developed aspergillosis compared with only four of 64 patients who had been on similar antibiotic regimens but who had retained nasal flora (p<0.008). Similarly topical nasal antibiotics may contribute to this. All our patients were at high risk (Table 1).

Initially the only clinical evidence of infection may be an unremitting fever, usually higher than 38°C. Dyspnoea and non-productive cough are often absent during the early stages. The reported incidence of pleuritic chest pain and pleural rub varies from 15 to 61 per cent [6, 10]. Our patients highlight the paucity and heterogeneity of the clinical signs and symptoms of invasive pulmonary aspergillosis (Table 1).
The chest radiograph may show no abnormality at the time the first symptoms develop. In one study, 10 per cent of patients who were shown to have lung disease at post mortem had had normal chest radiographs within the previous week [15]. The first radiological changes are often non-specific and would be compatible either with infection or infarction. Ventilation and perfusion isotopic lung scans help to exclude pulmonary embolism (Case 8). A discrete mass (Case 4) however, should alert the clinician to the possibility of invasive pulmonary aspergillosis. In this patient the radiological changes, seen in isolation from the clinical picture, were those of an invasive carcinoma. In one of our two patients who developed mycetomata there was no clinical or radiological evidence of pre-existing or residual pulmonary cavity. Cavitation may also emerge within areas of consolidation on sequential chest radiographs even though classical mycetoma formation does not occur, as in two other patients in our series. A diffuse interstitial pattern of pulmonary invasion has also been described in one case report [16].

Microbiological confirmation is difficult. Fifty per cent of patients with pulmonary disease produce no sputum [15], and two-thirds of those who do never grow aspergillus, whereas only 10 to 20 per cent of immunocompromised patients who do have positive sputum cultures will have aspergillosis. The finding of repeatedly positive culture, however, increases the likelihood of invasive pulmonary infection. A selective culture medium such as Sabouraud's dextrose agar, should be used routinely for culture in leukaemic patients in addition to less specialised media. A positive growth of aspergillus on nasal culture appears to have a predictive role. In one study [14] 10 of 11 patients with positive nasal cultures developed invasive pulmonary aspergillosis. However, negative nasal culture was of little value as eight of the 114 patients with negative nasal cultures still developed invasive pulmonary aspergillosis. In another study, none of the 34 patients with disseminated aspergillosis had positive blood cultures [11], although blood cultures have occasionally been positive in cases of aspergillus endocarditis [17]. We were unable to identify aspergillus either microscopically or on culture in any of our patients who did not come to autopsy. The diagnosis is therefore presumptive in our two surviving patients.

Standard serological tests used successfully in the diagnosis of allergic bronchopulmonary aspergillosis are almost never positive in the immunocompromised patient, as the level of antibody produced is too low. However, the use of concentrated serum in an immunodiffusion technique has been shown to be a specific, though not a sensitive test [18], as at least 30 per cent of patients fail to become seropositive. Other techniques including counter-immuno-electrophoresis [19], enzyme-linked immunoadsorbent assay [19], passive haemagglutination [20] and radioimmunoassay [21] support this finding. Immunoblot techniques have isolated an antibody to a 40 000 dalton component of the fungus present in 79 per cent of patients. However the antibody response declines as the disease becomes more advanced [22]. Techniques to detect the presence of specific components of the antigen are at a developmental stage [23-25].

An ante-mortem tissue diagnosis is therefore the ideal but the patients are often too ill, thrombocytopenic and hypoxic to withstand open-lung biopsy, although biopsy via fibreoptic bronchoscopy is safe and well tolerated [26, 27]. However a recent study found that it established or suggested the diagnosis in only 50 per cent of leukaemia patients. False-negative results are particularly likely early in the course of the disease [28].

Treatment often has to be started on clinical suspicion alone. Intravenous amphotericin B is the drug of choice. 5-Fluorocytosine may be synergistic when used in combination with amphotericin B [29, 30] but it can have a myelosuppressive effect especially if high serum levels develop due to amphotericin B-induced nephrotoxicity. A new absorbable triazole, intraconazole, has been shown to have activity in aspergillosis in a pilot study [31]. Most patients are treated with 1.5 to 2.0 g of amphotericin B over six to 12 weeks, although total doses given to
patients with invasive aspergillosis who have responded to treatment are reported from 0.11 g up to 3.1 g [32]. The maximum dose given to any of our patients was 1.15 g over three months. Clinical observations appear to be good indicators of response, though there have been some reported cases of relapse months later [33]. There is wide variation in the susceptibility of different strains in vitro to antifungal agents and no information is available to correlate the results of in vitro tests with the clinical outcome. The dose must be adjusted according to the tolerance of the individual patient, the major side effect of amphotericin B being nephrotoxicity. Concurrent oral amiloride will conserve potassium, though care must be taken not to induce hyperkalaemia [34]. The nephrotoxicity is reversible if detected early and the dose reduced. Serious cardiac arrhythmias such as occurred in Patient 5 are extremely rare [35].

Oral prophylaxis with non-absorbable antifungal agents is unlikely to reduce the rate of infection with aspergillus, as the main portal of entry is via the respiratory tract. However, an encouraging reduction in the incidence of invasive aspergillosis has been demonstrated following the use of prophylactic amphotericin B nasal spray [36]. Inadequate filtration of outside air is the main source of aspergillus spores in the hospital environment. Systems in use for filtering air in most modern hospitals can be expected to reduce the total spore count by approximately 33 per cent [37]. High-quality filters will remove all aspergillus spores. No cases of invasive aspergillosis have been reported in patients in isolation units [38]. Vacuuming and other processes which disturb the air will cause a large increase in the number of airborne aspergillus spores [39].

In the past the prognosis of invasive pulmonary aspergillosis was extremely poor. The first reports of successful treatment appeared just over a decade ago [40,41] and now several studies have demonstrated that a significant proportion of patients can be cured if treatment is started early. A study from Baltimore [42] has shown a cure in 50 per cent of patients, with a partial response in the other 50 per cent, when treatment was started within 96 h of pulmonary infiltrates appearing. All the patients in whom treatment was delayed two to three weeks after the onset of radiological signs died. This led to two studies, one of which is still in progress, where intravenous amphotericin B has been used empirically in patients who have a fever which has not responded after four to seven days of broad-spectrum antibiotics [43,44]. The numbers are as yet too small to be significant, although the mortality rate in the second study is slightly lower in the amphotericin B-treated group in which five out of 30 (17 per cent) died compared with seven out of 31 (22 per cent) in the untreated group. None of the deaths in the amphotericin B-treated group have been attributed to fungal infections compared with three out of seven in the control group. Although the number of patients in these series is small the results are encouraging.

ACKNOWLEDGEMENT

The secretarial assistance of Mrs Pamela Knowles and Miss Sandra Garth is greatly appreciated.

REFERENCES


33. Gercovich FG, Richman SP, Rodrigues V, Luna M, McCredie KB, Bodey GP. Successful

34. Prentice HG. Personal communication.


