Invasive pulmonary aspergillosis in an insulin-dependent diabetic

S. M. Janes, K. F. Barker, V. Mak and D. Bell*

Central Middlesex Hospital, Acton Lane, Park Royal, London NW10 7NS, U.K.

Introduction

Invasive pulmonary aspergillosis (IPA) occurs almost exclusively in patients with profound neutropenia (1), often secondary to the cytotoxic therapy used in the treatment of haematological malignancy or patients undergoing organ transplantation. Patients with severe defects in cell-mediated immunity may also develop IPA (2). More rarely, cases have been reported in non-immunocompromised individuals, associated with alcoholism, diabetes mellitus, steroid therapy and influenza virus infection (3–7). Mortality in patients with invasive aspergillosis may be as high as 90% despite antifungal therapy (8–12). We report a patient with diabetic ketoacidosis, who rapidly developed respiratory problems, but with early diagnosis of invasive pulmonary aspergillosis and aggressive treatment with dual antifungal therapy he survived, although he required 57 days in ITU.

Case Report

A 45-year-old insulin-dependent diabetic was admitted to hospital with a 1 week history of a 'flu-like' illness. In the 24 h prior to hospital admission he had become pyrexial with vomiting and confusion and consequently omitted his insulin. He had a past medical history of hypertension treated with enalapril, drank 10 units of alcohol per week, and had not taken antibiotics or steroids within the last year.

On admission his temperature was 38°C, pulse 100 min⁻¹, blood pressure 120/70, and was ketotic. Glasgow Coma Scale (GCS) was 9/15. His chest was clear and he had no focal neurology.

Initial blood electrolytes were as follows: sodium 140 mmol l⁻¹ (normal range 134–145), potassium 5.4 mmol l⁻¹ (3.5–5.0), urea 42 mmol l⁻¹ (3.0–6.7), creatinine 393 μmol l⁻¹ (76–120) and glucose 72 mmol l⁻¹ (3.5–10.0). Arterial blood gas (ABG) pH 7.14, PaCO₂ 26 mmHg, PaO₂ 102 mmHg, bicarbonate 9 mmol l⁻¹ (22–30). Full blood count, clotting screen, electrocardiograph and initial chest X-ray appearance were normal.

He was diagnosed and treated as a diabetic ketoacidosis, with intravenous fluid and insulin. Intravenous cefotaxime, flucloxacillin and metronidazole were commenced because of his pyrexia and possible aspiration. Although blood sugar, urea and acidosis all gradually corrected over the next 24 h, the sodium gradually rose to 175 mmol l⁻¹ at which time he was again noted to be confused with a deteriorating GCS and required elective ventilation for a compromised airway. The hypernatraemia was corrected over 4 days associated with a slow neurological recovery. A computed tomography-scan of head and ultrasound of kidneys were both normal.

Over this period the pyrexia continued despite intravenous antibiotics. Blood and urine cultures were negative. Bilateral antral washouts were performed for persistent nasal discharge and purulent material drained from the left maxillary sinus. By day 5 he became progressively more hypoxic and developed left-sided chest signs. The repeat chest X-ray showed new patchy consolidation in the left lower zone (Plate 1). The antibiotics were changed to piperacillin, gentamicin and metronidazole. As Candida albicans had been isolated from endotracheal aspirates taken on day 2 and day 3 of the admission, and from the antral washouts, intravenous fluconazole was commenced. Bronchoscopy was performed, and showed thick white plaques over the left main bronchus extending into left upper and lower lobe bronchi, thought to be consistent with
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PLATE 2. Magnification x 200, periodic acid-Schiff stain. Bronchial biopsy specimen showing connective tissue infiltrated by a mass of fungal hyphae which are both branching and septate and consistent with aspergillus.

candida. On day 1 Aspergillus fumigatus was isolated from endotracheal aspirates taken on day 4 and 5 and a repeat bronchoscopy was performed with bronchial biopsies. Chest X-ray appearance and gas exchange continued to deteriorate and fluconazole was replaced by oral itraconazole 200 μg b.d. and amphoterin nebulizers 40 μg b.d. By day 10 A. fumigatus had been isolated from bronchial washings and invasive pulmonary aspergillosis was confirmed by biopsy (Plate 2). In view of his impaired renal function intravenous amphotericin B colloidal dispersion (ABCD) ["Amphocil"] was commenced at 2 mg kg⁻¹ daily increasing to 4 mg kg⁻¹ daily.

The isolate A. fumigatus was sensitive to both amphotericin and itraconazole with minimum inhibitory concentrations of 0.125 mg l⁻¹ and 0.25 mg l⁻¹, respectively. Serum itraconazole levels taken 2 weeks after commencing therapy, and at intervals thereafter, were satisfactory. Serological testing showed a strongly positive titre for influenza B virus (1:640). Other respiratory serology was normal. An HIV antibody test was negative and immunology was normal. Aspergillus precipitins were negative. Initially his chest X-ray continued to deteriorate (Plate 3) but after 57 days ventilation and 37 days of ABCD, he was discharged from ITU. He later received a further 23 days of ABCD when A. fumigatus was again isolated from respiratory specimens. Itraconazole was continued for 6 months. He made a good clinical recovery and returned to full-time employment 3 months later. Discharge CT scans showed persistent scarring and cystic changes in the anterior segment of the upper lobe (Plate 4).

Discussion

Aspergillus sp. are ubiquitous environmental fungi. Inhalation of air-borne conidia may result in harmless colonization of the respiratory tract, aspergilloma formation, allergic bronchopulmonary aspergillosis or invasive pulmonary aspergillosis. The incidence of invasive disease is variable and unpredictable, even in the highest-risk neutropenic population.

This is an unusual case of a non-immunocompromised patient developing, most probably, hospital-acquired invasive pulmonary aspergillosis (IPA). Of the 39 previously reported cases (4–6, 13–19) of non-immunocompromised patients with IPA only three were diabetic and all were non-insulin dependent (5, 6, 13). Five of the 39 cases had concurrent influenza virus infection, all type A unlike our type B (4, 5, 16, 18, 19). Influenza possibly predisposes to IPA via damage to the respiratory mucosa, or suppression of cell-mediated immunity (20).

Opportunistic infections are more common in patients with diabetes mellitus, particularly insulin-dependent diabetics, with one or more major complication of the disease. In vitro studies have shown decreased leukocyte bactericidal activity and impaired macrophage mobility and phagocytic...
from respiratory secretions of patients with patchy consolidation plus histology. Although diagnostic value.

Several amphotericin preparations are helpful in the diagnosis of invasive disease, and serological studies are now available permitting the use of much higher daily and total doses (over 20 g in this patient). Itraconazole, although active against *Aspergillus* sp., was, at this time, only available in oral formulation. Concern has been expressed about poor absorption and hence sub-optimal serum and tissue levels (26). Denning et al. (27) report a 11% clinical, radiographical and mycological cure in 51 patients with invasive aspergillosis treated with itraconazole alone. Six of these patients were non-immunocompromised with total cure in three cases. Fluconazole has negligible activity in these infections.

This case illustrates an unusual complication of diabetes mellitus and it is likely that the combination of recent influenza B combined with diabetic ketoacidosis provided the setting for colonization and subsequent invasion of the bronchi by aspergillus. His fever was never adequately explained and hence an aggressive approach to diagnosis was adopted. It would appear that early intervention, confirming the diagnosis of invasive pulmonary aspergillosis, and initiating early treatment with dual therapy of ABCD and itraconazole have led to a full recovery of this patient despite a prolonged stay in ITU. He remains with left upper lobe bronchiectasis and possibly the risk of aspergilloma in the future and will continue to be monitored.

### References

Endobronchial non-Hodgkin’s lymphoma

W. M. McRae, C. S. Wong and G. M. Jeffery

Department of Medicine, Dunedin Hospital, Dunedin, New Zealand

Introduction

Non-Hodgkin’s lymphomas are a heterogeneous group of lymphoproliferative malignancies with different behaviour patterns, prognosis and management.

Non-Hodgkin’s lymphoma involves the thoracic structures, particularly the mediastinum and lung parenchyma, in up to 43% of patients at some stage in the course of their disease (1). Endobronchial involvement, however, is extremely rare, even in the presence of advanced disease.

The first report of endobronchial non-Hodgkin’s lymphoma was made by Dawe in 1955 (2). Since this time less than 50 cases have been described in the literature (3-6).

We report a further case and review the relevant literature.

Case Report

A 56-year-old man presented with a 3 months’ history of dyspnoea and productive cough. He had experienced 5 kg weight loss in the preceding year, mild night sweats, but no associated fevers. He had a 40 pack-year smoking history.

The chest radiograph showed consolidation at the right lower and middle lobes with widened mediastinum suggestive of lymphadenopathy (Plate 1). Computed tomography (CT) scan of the chest demonstrated extensive mediastinal and right hilar lymphadenopathy, distal parenchymal consolidation in the right lower lobe and a large right basal pleural fluid collection.