Wheeze in a heart transplant patient with lymphoma

Mangalam Sridhar, Michael Jeffers, Eamonn Brankin, Michael Soukop, Stephen Banham

Summary

We report a case of wheeze in a heart transplant patient who was receiving chemotherapy for a transplant-associated lymphoma. The patient was in severe respiratory distress; there were no radiological abnormalities. A diagnosis of invasive bronchopulmonary aspergillosis was made by bronchoscopy and bronchoalveolar lavage. Despite prompt antifungal therapy the patient died.

Wheeze in a non-asthmatic immunocompromised patient, even in the absence of radiological abnormalities, is highly suggestive of invasive bronchopulmonary aspergillosis. Diagnosis is best established by bronchoscopy and examination of the fluid obtained by bronchoalveolar lavage; currently the response to treatment is often disappointing.

Keywords: wheeze, bronchopulmonary aspergillosis, immunocompromise

Immunocompromise resulting from bone marrow suppression by chemotherapeutic agents and immunosuppressive drugs, including corticosteroids, often allows an infection by fungal, protozoan and other opportunistic pathogens. Pneumonia caused by these agents accounts for 50–60% of the deaths in immunocompromised patients.¹ Immunosuppression also blunts the inflammatory response, leading to difficulties in the diagnosis of infection and delays in the institution of appropriate therapy. In most instances significant involvement of the respiratory tract in an opportunistic infection is characterised by fever, cough, breathlessness, and the presence of pulmonary infiltrates in the chest radiograph. Occasionally the presentation is atypical and a high index of suspicion with an awareness of the more unusual presentations of the illnesses is required if an early diagnosis is to be made. We present here the case of a heart transplant patient undergoing chemotherapy for gastric lymphoma in whom wheeze was the only sign of an eventually fatal attack of invasive bronchopulmonary aspergillosis.

Case report

A 61-year-old man was referred to the Medical Oncology department for treatment of a non-Hodgkin's lymphoma. He had undergone a

successful heart transplantation seven years previously at Papworth Hospital for a viral cardiomyopathy and had since been on immunosuppressive therapy with azathioprine and cyclosporin. He was a non-smoker and was not known to be asthmatic. Symptoms of abdominal pain, weight loss and vomiting led to investigations which resulted in a diagnosis of a gastric non-Hodgkin's lymphoma. The lymphoma was WHO intermediate grade, B-cell centroblastic and *in situ* hybridisation for Epstein–Barr virus was negative.

A distal gastrectomy was performed and at operation the tumour was found to be densely adherent to the pancreas. Two 2-cm liver metastases were also noted. In view of the residual tumour it was decided that the patient would be given chemotherapy by the VAPEC-B regime (vincristine, adriamycin, prednisolone, etoposide, cyclophosphamide and bleomycin), plus co-trimoxazole, ketoconazole, allopurinol and cimetidine for the duration of therapy. After a prolonged but uneventful recovery from surgery the patient was given 50 mg of prednisolone and 200 mg of ketoconazole a day, two tablets twice a day of co-trimoxazole, a pulse of adriamycin and cyclophosphamide followed a week later by a pulse of vincristine and bleomycin as per the regime. After the second pulse of chemotherapy the patient became unwell and was hospitalised with acute renal failure and high cyclosporin levels. The condition was treated with dopamine and intravenous fluid therapy. Renal function improved but the patient became pyrexial. Blood culture from a central venous catheter grew staphylococci and the patient became afebrile after removal of the central venous line and treatment with antibiotics. A few days later he became generally unwell once more, complaining of tiredness and malaise. He also had a mild cough but was afebrile. There were signs of herpetic ulceration in the oral cavity as well as oral candidiasis. Examination of his chest revealed bilateral wheeze even whilst he was on 50 mg of prednisolone a day. A chest radiograph showed no abnormality. White cell count was $0.4 \times 10^9/l$. Blood and urine cultures were negative.

In view of the deteriorating clinical situation and persistent wheeze, despite the normal chest radiograph, the patient underwent bronchoscopy. This showed membranous lesions in the bronchial tree and a cytological examination of fluid obtained by bronchoalveolar lavage

Glasgow Royal
Infirmary, Alexandra
Parade, Glasgow
G4 0SF, UK
Department of
Respiratory Medicine
M Sridhar
S Banham
Department of
Pathology
M Jeffers
Department of
Medical Oncology
E Brankin
M Soukop

Accepted 4 January 1995

revealed numerous characteristically branching septate hyphae of *Aspergillus* sp. (figure). The patient was started immediately on liposomal amphoterecin, but despite intensive inotropic and ventilatory support died four days later. *Post mortem* examination showed extensive membranous infiltration of the bronchi and nodular infiltration of the lung parenchyma by *Aspergillus* organisms. There were no tumour deposits in the liver.

Discussion

Our case highlights the significance of the clinical sign of wheeze as an indicator of invasive bronchopulmonary aspergillosis in immunocompromised patients. In most immunocompromised patients life-threatening opportunistic infections of the respiratory tract cause fever, breathlessness, cough and pulmonary infiltrates on the chest radiograph.¹ In our patient the only sign of what eventually transpired to be a fatal attack of aspergillosis was a striking wheeze which appeared even as the patient was on 50 mg of prednisolone a day. Although the patient had a cough he was afebrile and there were no abnormalities noticeable on the chest radiograph. It is believed that the wheeze in invasive bronchopulmonary aspergillosis results from narrowing of the tracheobronchial tree by pseudomembranes² which were a striking feature in this case. Although nodular pulmonary infiltrates were noted at *post mortem*, in

Figure Microscopic view of fluid obtained by bronchoalveolar lavage showing characteristic septate hyphae of *Aspergillus* (methenamine silver stain; magnification $\times 630$)

7–10% of cases of invasive bronchopulmonary aspergillosis the disease is restricted to the tracheobronchial tree, without any parenchymal involvement.³ Occasionally the lesions and the wheeze may be unilateral.⁴ Diagnosis usually requires bronchoscopy and identification of a large number of characteristic fungal hyphae in the bronchoalveolar lavage fluid. Interpretation of positive sputum cultures of the organism is rendered difficult by the fact that these fungi are quite commonly present in sputum as contaminants, although some workers have suggested that in immunocompromised patients the presence of these organisms in sputum is always significant and warrants therapy.⁵ Transbronchial lung biopsy and demonstration of invasion of the lung parenchyma by the fungi is complicated by the frequently coexistent thrombocytopenia and is not usually required. Identification of fungal hyphae in endobronchial biopsies of membranous lesions seen in the tracheobronchial tree is probably a safer but equally reliable method of securing the diagnosis.

Our report serves to highlight the dismal prognosis of granulocytopenic patients suffering from invasive aspergillosis. Mortality from invasive aspergillosis in the setting of neutropenia and immunosuppression approaches 90%.⁶ While delay in the diagnosis may in part explain this unsatisfactory situation, recent reports suggest that even the most intensive anti-fungal therapy is ineffective when started after clinical illness is obvious.⁷ Liposomal preparations of amphoterecin which achieve 10-fold higher plasma levels when compared with conventional preparations have been shown to be of value in certain cases but the overall prognosis of an immunocompromised patient with invasive aspergillosis remains unacceptably poor. Prevention of infection by reduction of airborne infection is presently considered the best strategy in dealing with the disease.⁸

Our presentation also draws attention to the problem of lymphoproliferative disorders in post-transplant patients on immunosuppressive therapy.⁹ Recent studies have confirmed that these patients are at a risk of developing non-Hodgkin's lymphoma and that the risk is directly related to the intensity of immunosuppression, with patients on azathioprine and cyclosporin being at a greater risk than patients on either drug alone.¹⁰ Whilst in appropriate cases withdrawal of immunosuppressive therapy, acyclovir and surgical resection will

Invasive bronchopulmonary aspergillosis

- immunosuppressed patients are at high risk of developing fungal infections
- unexplained wheeze may be the sole presenting symptom of invasive bronchopulmonary aspergillosis
- diagnosis of bronchopulmonary aspergillosis is secured by bronchoscopy, bronchoalveolar lavage, endobronchial biopsy of membranous lesions or a transbronchial lung biopsy
- treatment is with intravenous amphoterecin, but the prognosis is poor

Immunosuppression and cancer

- post-transplant patients on immunosuppression therapy are at risk of developing non-Hodgkin's lymphoma
- the risk of developing a lymphoma is related to the intensity of immunosuppression
- in some cases stopping immunosuppression drugs and giving anti-viral therapy will result in resolution of the lymphoproliferative disorder

result in resolution of the condition, these measures are not always feasible or successful.⁹ Conventional treatment for lymphoma in these patients poses unique problems as the combination of chemotherapy-induced neutropenia and immunosuppressive drug therapy leads to a degree of compromise of immune status that often results in a lethal opportunistic infection, as in our case.

In conclusion, wheeze in an immunocompromised patient, even in the absence of radiological abnormalities, may be a sign of invasive bronchopulmonary aspergillosis. Bronchoscopy, examination of the bronchoalveolar lavage fluid and biopsy of the membranous lesions identified during bronchoscopy secure the diagnosis but the response to anti-fungal treatment is usually poor.

- 1 Fanta CH, Pennington JE. Pneumonia in the immunocompromised host. In: Pennington JE, ed. *Respiratory infections: diagnosis and treatment*. New York: Raven, 1983; p 171.
- 2 Hall J, Heimann P, Costas C. Airway obstruction caused by aspergillus tracheobronchitis in an immunocompromised patient. *Crit Care Med* 1990; 18: 575-6.
- 3 Young RC, Bennett JE, Vogel CL, Carbone PP, De Vita VT. Aspergillosis. The spectrum of the disease of 98 patients. *Medicine* (Baltimore) 1970; 49: 147-73.
- 4 Tait RC, O'Driscoll BR, Denning DW. Unilateral wheeze caused by membranous aspergillus tracheobronchitis in the immunocompromised patient. *Thorax* 1993; 48: 1285-7.
- 5 Nalesnik MA, Myerowitz RL, Jenkins R, Lenkey J, Herbert D. Significance of aspergillus species isolated from respiratory secretions in the diagnosis of invasive pulmonary aspergillosis. *J Clin Microbiol* 1980; 11: 370-6.
- 6 Fisher BD, Armstrong D, Yu B, Gold JWM. Invasive aspergillosis. Progress in early diagnosis and treatment. *Am J Med* 1981; 71: 571-7.
- 7 Munier F. Fungal infections in the compromised host. In: Rubin R, Young L, eds. *Clinical approach to infection in the compromised host*. New York: Plenum, 1988; pp 193-220.
- 8 Ettinger NE, Trulock EP. Pulmonary considerations of organ transplantation. Part 2. *Am Rev Respir Dis* 1991; 144: 213-23.
- 9 Nalesnik MA, Makowka L, Starzl TE. The diagnosis and treatment of post transplant lymphoproliferative disorders. *Curr Probl Surg* 1988; 25: 371-472.
- 10 Oplez G, Henderson R for Collaborative Transplant Study. Incidence of non-Hodgkin's lymphoma in kidney and heart transplant recipients. *Lancet* 1993; 342: 1514-6.

Gastrointestinal haemorrhage associated with free-base (crack) cocaine

DA Fennell, SS Gandhi, BNC Prichard

Summary

We report a case of a crack user presenting with chronic gastrointestinal haemorrhage due to deep gastric ulceration; the putative aetiology being predictable from this agent's pharmacology.

Keywords: crack cocaine, haemorrhage, gastric ulceration

The spectrum of multisystem toxicity for cocaine and the alkaloid free base 'crack' includes gastropyloric,¹ duodenal ulceration, and perforation.² Its heat stability, conferred by dissociation of the hydrochloride moiety during transformation from cocaine to free base, underlies its pharmacokinetic behaviour, providing (via inhalation) extremely efficient drug delivery.³ The fast (below 30 s) rise to peak plasma concentration of this potent sympathomimetic during smoking potentially predisposes the user to systemic ischaemic pathology.

Case report

A 34-year-old male primary crack user presented with a one-week history of melaena, haematemesis and epigastric pain. There was no recent history of non-steroidal anti-inflammatory use, and although a cigarette smoker (20 per day) there was no previous nor familial history of peptic ulcer disease. He had

recently been smoking crack cocaine on a daily basis. On examination, he was afebrile, haemodynamically stable, but profoundly anaemic (haemoglobin 4.8 g/dl, mean corpuscular volume 90 fl), with generalised upper abdominal tenderness, and evidence of melaena. Urgent upper gastrointestinal endoscopy identified a very deep ulcer (with no evidence of scarring) localised at the incisura, which was injected with adrenaline. The patient discharged himself 48 hours after admission.

Clinical features of crack use

Pharmacokinetics

- rapid absorption via inhalation
- eliminated by plasma esterases; half-life 50 min

Pharmacodynamics

- euphoria
- sympathetic activation (ie, tachycardia, peripheral vasoconstriction)
- intense psychological dependence

Toxicity

- convulsions
- psychotic symptoms
- hyperthermia
- multisystem pathology secondary to vasospasm (eg, cutaneous, myocardial, cerebral, bowel infarction)

Division of Clinical Pharmacology, University College Hospitals Medical School, The Rayne Institute, University Street, London WC1E 6JJ, UK
DA Fennell
SS Gandhi
BNC Prichard

Correspondence to DA Fennell, Division of Gastroenterology, Department of Medicine, Royal Postgraduate Medical School, The Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

Accepted 9 December 1994