

This report suggests that directly instilled rhDNase may be one alternative to conventional therapy for lobar atelectasis. Its use may be beneficial for the subset of patients with lobar atelectasis due to retained secretions which fail to clear with vigorous coughing, chest physiotherapy, and suctioning. Direct bronchoscopic instillation offers the advantage of concentrating it at the site of obstruction and avoids the delay of waiting for the effects of nebulised administration. Further study is warranted comparing rhDNase by direct instillation and nebulisation with traditional respiratory therapy for lobar collapse due to retained secretions.

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Thorax 1995;50:1321-1323

Use of nebulised liposomal amphotericin B in the treatment of *Aspergillus fumigatus* empyema

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Abstract

A 28 year old man with asthma, bronchopulmonary aspergillosis, pulmonary thromboembolic disease, and pulmonary hypertension developed *Aspergillus fumigatus* empyema complicating a pneumothorax. His condition progressively deteriorated despite treatment with intravenous and intrapleural amphotericin B, but improved promptly after substituting nebulised liposomal amphotericin B and oral itraconazole. This experience suggests that nebulised liposomal amphotericin B is well tolerated and merits further assessment in the treatment of pulmonary fungal disease.

(*Thorax* 1995;50:1321-1323)

Keywords: *Aspergillus fumigatus*, empyema, liposomal amphotericin B, nebuliser.

Aspergillus empyema is a rare condition which predominantly affects patients with chronic lung damage associated with previous tuberculosis and immunocompromised hosts.¹ Liposomal amphotericin B (AmBisome) is an effective agent for the treatment of patients with systemic fungal disease and has been reported as having less toxicity than amphotericin

when given intravenously.² We report the first clinical use of liposomal amphotericin B delivered directly to the lungs using a nebuliser.

Case report

A 28 year old man had presented seven years previously with increasing dyspnoea. He was known to have asthma which had been well controlled and examination suggested the presence of pulmonary hypertension. Investigation including echocardiography, radionuclide imaging, and cardiac catheterisation was performed which confirmed the presence of moderately severe pulmonary hypertension; no cause was identified. A diagnosis of unexplained or primary pulmonary hypertension was made and he was anticoagulated with warfarin.

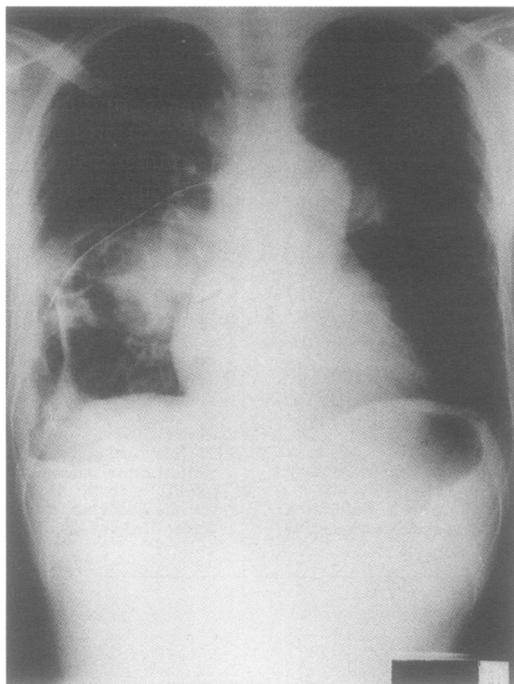
There was a slow gradual deterioration in his exercise tolerance to New York Heart Association III over the next seven years until he presented as an emergency with severe haemoptysis. A chest radiograph at this time demonstrated a cavitating lesion in the left mid zone. His *Aspergillus* precipitins were strongly positive and he was referred for further assessment and management. A contrast enhanced thoracic computed tomographic scan revealed extensive central pulmonary artery thrombosis and evidence of a mycetoma within a cavity. Lower limb venography showed the presence of venous thrombosis and the cause of his pulmonary hypertension was diagnosed as chronic subacute massive pulmonary embolism. The source of the haemoptysis was thought to be an aspergilloma within an old cavitating pulmonary infarct. Bronchial angiography with embolisation of the vessels supplying the cavity was performed, followed by right heart catheterisation and infusion of streptokinase and plasminogen directly into the pulmonary artery.³ There was no change in his pulmonary vascular resistance or pressure and pulmonary endarterectomy and insertion of an

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Reprint requests to:
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Received 13 January 1995
Returned to authors
6 March 1995
Revised version received
13 April 1995
Accepted for publication
18 April 1995



Chest radiograph with intercostal drain in situ before treatment with nebulised liposomal amphotericin B. A right sided empyema can be seen with adjacent consolidation and cavitation. The right ventricle and pulmonary arteries are enlarged.

inferior vena cava filter was carried out. He was established on warfarin and aspirin and discharged back to his referring hospital.

Twelve months later he was readmitted with a right pneumothorax, pyrexia, and purulent sputum. An intercostal drain was inserted which continually drained purulent fluid and air, indicative of a bronchopleural fistula (figure). The sputum and pleural fluid were positive for *Aspergillus fumigatus* on culture. All other microbiological culture and serological tests (including mycobacteria) were negative, and there was no evidence of an immunocompromised state. He was commenced on intravenous amphotericin B, 1 mg/kg/day, and intrapleural amphotericin B, 20 mg twice daily, via the intercostal drain. After two weeks of treatment he had not improved and cultures remained positive for *Aspergillus*; moreover, his serum creatinine level had risen from 79 to 164 $\mu\text{mol/l}$. This was regarded as treatment failure and the medication was changed to oral itraconazole, 400 mg/day, and nebulised amphotericin B, 50 mg twice a day via a Turboturrett 2 nebuliser with a driving flow of 8 l/min. The amphotericin B had to be discontinued because it precipitated severe bronchospasm despite premedication with salbutamol. Accordingly, liposomal amphotericin B was substituted at a dose of 50 mg twice daily with no bronchospasm. Within three days of starting this treatment the patient became afebrile and after four weeks all sputum and pleural fluid cultures were negative for *Aspergillus*. The intercostal drain was removed by the fifth week and treatment discontinued after six weeks. There has been no relapse after one year of follow up.

Discussion

This case reports the first successful use of nebulised liposomal amphotericin B in the treatment of *Aspergillus* empyema complicating a bronchopleural fistula. *Aspergillus* empyema is an uncommon condition and is associated with previous tuberculous infection, thoracic surgery, or cytotoxic therapy.¹ The most likely source of the empyema presented here is rupture of a cavitating pulmonary infarct colonised by *Aspergillus fumigatus*. The patient was a known asthmatic and the presence of a peripheral eosinophilia, high serum IgE, and positive skin prick tests to *Aspergillus* supported the diagnosis of bronchopulmonary aspergillosis in addition to the aspergilloma.

Use of conventional therapy with intravenous and intrapleural amphotericin B failed to control the *Aspergillus* infection and, moreover, led to a doubling of the creatinine level. Liposomal amphotericin B has been shown to be effective when given intravenously to immunocompromised patients who have failed to respond to conventional amphotericin B.⁴⁻⁶ It has also been shown to cause less nephrotoxicity.² We chose to administer amphotericin B via the nebulised route because we wished to deliver a high concentration to the lung and felt that the large bronchopleural fistula may lead to direct entry to the pleural space. Indeed, amphotericin activity was detected in the pleural fluid by an imidazole resistant *Candida glabrata* bioassay after 3–8 days of treatment, after which time there was insufficient pleural fluid for the assay to be performed.

Our patient could not tolerate nebulised amphotericin B because it induced bronchospasm. He was, however, able to tolerate nebulised liposomal amphotericin B and this is the first recorded use of this product in nebulised form in humans. A liposomal vehicle has, however, been well recognised as an attractive means of delivering drugs to the lungs.⁷

The role of nebulised liposomal amphotericin B in the successful management of this patient cannot be fully evaluated because of the concomitant administration of itraconazole which has been shown to be effective in a variety of *Aspergillus* infections,⁸ and we do not suggest that this report proves an efficacy for liposomal amphotericin B as monotherapy, or even as part of combination therapy, in *Aspergillus* empyema. We can report that nebulised liposomal amphotericin B was well tolerated by this asthmatic patient and did not lead to any unwanted side effects throughout the six week course of treatment. In particular, renal function was seen to improve to normal levels and there was no hypokalaemia or rise in alkaline phosphatase levels. There was no detrimental effect on pulmonary function. Unfortunately, at approximately £10 000 for the six week course, liposomal amphotericin B was an expensive alternative to conventional amphotericin therapy which would have cost £300 for six weeks at a dosage of 1 mg/kg/day.

Formal studies of nebulised liposomal amphotericin B should be considered to define its role in the management of *Aspergillus* pulmonary conditions.

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Thorax 1995;50:1323

Commentary

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These three cases are at first sight completely different, but there is an important common theme. In each instance an unconventional and expensive treatment was given when all else had failed and the results were gratifyingly successful. This begs the question, common to all case reports, whether they are illustrative and helpful for the management of other patients, or whether they simply represent an amazing coincidence which has been given spurious respectability by being published. The clinical teams should be congratulated on their ingenuity and persistence, but did the management change actually contribute to the improvement or was it simply a way of structuring time (at considerable expense) until nature did the job?

The case presented by Codispoti *et al* (pp 1317-9) describes the use of extracorporeal membrane oxygenation (ECMO) to support a patient dying of pneumococcal pneumonia until treatment was effective. The key question here is whether or not she could have survived the six days of ECMO support with conventional ventilation. The reason given for starting ECMO was that the haemodynamic and ventilatory parameters were considered incompatible with survival. If we assume this judgement to be correct, then ECMO undoubtedly saved her life. Previous studies of ECMO in randomised trials have shown no benefit, but the failure of a treatment for a randomised group does not mean that the treatment could never be helpful to anyone. The lesson from this report is that ECMO should be considered as a last ditch means of ventilatory support when there are very good grounds to predict eventual recovery. Such cases are probably very few, and it is essential that this report is not used as an argument for an expensive escalation in preterminal treatment for those patients with no hope of survival.

The second report by Touleimat *et al* (pp 1319-21) suggests that instillation of DNase via a bronchoscope to an area of the lung subject to recurrent collapse from sputum retention is worthwhile. The description of the results "... rapid dissolution of sputum and

opening of the orifice . . ." is more in line with reporter enthusiasm than enzyme kinetics. Also, at first sight it is difficult to see how a single DNase treatment with clearing of sputum could have a lasting effect when aspiration of the plug previously did not. It is conceivable, however, that DNase allowed clearance of more peripheral airways and thus promoted better ventilation and clearance to prevent subsequent sputum plugging. DNase is expensive for chronic treatment but a single dose is not, and this report certainly suggests a possible indication for a new drug over and above that which has been established in clinical trials. It is interesting to speculate whether nebulised DNase would have been equally successful, avoiding repeat bronchoscopies with the cost and inconvenience involved.

The final case report described by Purcell and Corris on pp 1321-3 is the most difficult to believe. In this, nebulised liposomal amphotericin apparently sterilised the pleural space when intrapleural instillation of amphotericin had failed. Even if the patient did have a large bronchopleural fistula, this still sounds a singularly inefficient way of getting a drug into this compartment. Either there is some additional therapeutic benefit from putting the drug into a liposome, which is highly unlikely, or the itraconazole that was given at the same time was actually responsible for the improvement. Either way the main interest of the report, as the authors point out, is that the liposomal form of amphotericin did not provoke asthma when the conventional form had done so, and there may well be other situations in which liposomal amphotericin by nebuliser would be worth considering.

Taken together, these reports are useful for clinicians to remember when they have a very difficult case on their hands. It is, however, essential that these approaches are applied intelligently and are not used as an excuse for mindless expense. Controlled clinical trials are valuable for common problems but cannot address rare and difficult management issues such as these. This is the true value of case reports.