Lobar atelectasis in cystic fibrosis and treatment with recombinant human DNase I

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Introduction

Lobar atelectasis occurs in 4–11% of patients with cystic fibrosis (CF) (1,2). A large proportion of these do not resolve despite intensive medical treatment. A 31-year-old patient with CF developed a right upper lobe atelectasis which was resistant to conventional medical treatment. Two months later he was started on recombinant human DNase I (rhDNase) which was associated with partial resolution of the atelectasis and reduction in sputum viscoelasticity.

Case Report

A 31-year-old male with CF who suffered from recurrent respiratory infections presented with increased sputum production, dyspnoea, night sweats and fevers. He produced approximately 50 ml of thick tenacious sputum daily. His lung spirometry was forced vital capacity (FVC) of 2.45 l, and forced expiratory volume in one second (FEV₁) of 1.1 l. Chest radiograph showed right upper lobe collapse, cystic changes and ring shadows of bronchiectasis. There was no blood eosinophilia, aspergillus precipitins were negative and full viral, mycoplasma and legionella infection screens were negative. Sputum culture grew mucoid Pseudomonas aeruginosa. Intravenous antibiotics, systemic bronchodilators, steroids and intensive physiotherapy were administered. The patient received a combination of intravenous antibiotics which included azlocillin, ceftazidime, imipenem, and aminoglycosides for a total of 31 days. In addition he continued on his prophylactic nebulized antibiotics. Physiotherapy consisted of postural drainage and active cycle of breathing exercises including the forced expiratory technique. This was augmented with nebulized hypertonic saline and intermittent positive pressure breathing with the Bird ventilator for a period of 27 days. The patient also underwent bronchoscopy. Thick sputum plugs were aspirated by a very experienced bronchoscopist, no endobronchial lesion was seen but the chest radiograph following the procedure remained unchanged. Failure of medical treatment prompted a second bronchoscopy. Fewer secretions were seen on this occasion but the right upper lobe failed to re-expand.

Two months later the patient was treated with rhDNase 2.5 mg nebulized twice daily as part of a clinical trial. Chest radiograph prior to commencing rhDNase still showed the right upper lobe collapse [Plate 1(a)]. His FVC was 3.06 l and FEV₁ 1.13 l. He did not receive intravenous antibiotics or intensive physiotherapy 15 days prior to commencement on rhDNase. After about 2 weeks of treatment the patient started producing copious amounts of sputum (approximately 150–200 ml daily). He developed chest pain on the anterior aspect of the right side of his chest and was more breathless. Spirometry on day 14 of treatment with rhDNase was FVC 3.28 l and FEV₁ 1.12 l. Sputum production started to decrease and on day 28 a repeat chest radiograph showed partial re-expansion of the right upper lobe [Plate 1(b)].

Fresh sputum samples were obtained on presentation, pre-treatment with rhDNase and on day 28 of treatment with rhDNase and stored at −20°C. The dynamic storage modulus (G'), which reflects the elasticity of the sample, and the dynamic loss modulus (G''), which is related to viscosity of the sputum samples was measured using oscillatory analysis on a parallel plate rheometer (CSL 100, Carri-Med UK) (3,4). Viscoelasticity was similar for the samples obtained at presentation and after conventional treatment but significantly reduced after treatment with rhDNase (Fig. 1).
Plate 1 Chest radiograph prior to treatment with rhDNase showing right upper lobe collapse (a) and post treatment with rhDNase for 28 days showing resolution of right upper lobe collapse (b).

Fig. 1 Dynamic elasticity (a) and dynamic viscosity (b) of sputum samples obtained at (■) presentation, (♦) pre-treatment with rhDNase, and (▲) on day 28 of treatment with rhDNase. A significant reduction of sputum elasticity ($P<0.0001$) and sputum viscosity ($P<0.0001$) occurred following treatment with rhDNase compared to pre-treatment.

Discussion

Lobar atelectasis is a well documented complication of CF. The pathophysiology may be a combination of bacterial infection and the presence of endobronchial obstruction with a thick viscous exudate. Conventional medical treatment consists of antimicrobial therapy and vigorous pulmonary physiotherapy. Intermittent positive pressure breathing and nebulized hypertonic saline has been used to facilitate sputum expectoration (5). Bronchoscopy has been utilized for both diagnostic and therapeutic purposes. Unfortunately in this patient the above treatments had little effect.

The high sputum viscosity found in patients with CF has been attributed to the presence of deoxyribonucleic acid (DNA). The DNA is derived almost entirely from disintegrated neutrophils (6,7,8). RhDNase has been shown to reduce the viscosity of CF sputum in vitro by depolymerizing DNA (9).

In our patient treatment with rhDNase resulted in a remarkable reduction of sputum viscosity. Following sufficient treatment the persistent endobronchial obstruction due to thick tenacious secretions was relieved. This was reflected in the partial resolution of the right upper lobe atelectasis.

Lobar atelectasis in CF is difficult to treat and in some patients may progress to severe irreversible bronchiecstasis. Some individuals may even require
a lobectomy. RhDNase reduces viscoelasticity of secretions in CF and may in particular significantly improve the treatment of CF patients with lobar atelectasis.

References