Cyclophosphamide in severe steroid-resistant bronchiolitis obliterans organizing pneumonia

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A patient receiving carbamazepine and imipramine presented with severe bronchiolitis obliterans organizing pneumonia (BOOP). He developed progressive respiratory failure in spite of high-dose steroid treatment. Cyclophosphamide was given as adjunctive therapy, and a rapid improvement was seen. The authors suggest that an early therapeutic trial of cyclophosphamide should be considered in patients with BOOP who fail to respond to steroids.

Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) is increasingly recognized as a distinct clinicopathological entity (1). A rapid response to corticosteroid treatment and a generally favourable outcome were characteristic features of the initial description of BOOP (1,2). However, with increasing experience of the clinical spectrum of this disease, it is now recognized that some patients have rapidly-progressive disease, which is refractory to steroids and associated with a poor prognosis (3). The present case report describes the adjunctive use of cyclophosphamide in a patient taking carbamazepine and imipramine who developed severe steroid-resistant BOOP.

Case Summary

A 49-year-old, non-smoking male presented with a 3-week history of progressive dyspnoea with malaise, anorexia, weight loss, sweats and a non-productive cough. Nine months previously, he had been commenced on imipramine 100 mg and carbamazepine 200 mg once daily for depression. He had not been exposed to known toxins or relevant respiratory antigens. On examination, he was pyrexial (38.0°C) and had an erythematous rash over the trunk and limbs. He was tachypnoeic with symmetrically-reduced lung expansion and diffuse lung crackles. Examination was otherwise normal with no signs of connective tissue disease.

A chest radiograph demonstrated moderate bilateral symmetrical interstitial and alveolar shadowing most extensive at the lung bases. High-resolution computed tomography defined multiple areas of air-space consolidation with ground glass opacities but no hilar adenopathy (Plate 1). Arterial blood gas analysis on air showed PaO₂ 7.7 kPa and PaCO₂ 5.0 kPa. Forced expiratory volume in 1 s (FEV₁) was 1.70 (predicted 4.18) and functional vital capacity (FVC) 1.84 (predicted 5.24). He was too dyspnoeic for full spirometry. Serological tests for viruses, atypical organisms, hepatitis, human immunodeficiency virus (HIV), collagen vascular and autoimmune disease were negative. Avian and fungal precipitins were negative. Liver function tests were abnormal. Skin biopsy showed non-specific dermatitis. Fibre-optic bronchoscopy with transbronchial biopsy was performed. The biopsy specimen showed a patchy interstitial lymphocytic infiltrate with severe pneumocyte hyperplasia, the alveoli and alveolar ducts were filled with buds of fibroblastic tissue characteristic of BOOP.

Prednisolone 1 mg kg⁻¹ day⁻¹ (60 mg) was commenced, and imipramine and
carbamazepine were discontinued. The patient’s condition continued to deteriorate with worsening respiratory failure and progression of the radiographic shadowing over the next 3 weeks. At this time, an FiO₂ of 60% produced an arterial PaO₂ of 6·0 kPa and mechanical ventilation was considered. Cyclophosphamide 150 mg day⁻¹ was then added, and by Day 7 of this treatment, the patient’s condition had begun to improve.

The patient made a dramatic recovery over the next 6 weeks. His arterial blood gas analysis on air showed PaO₂ 12·5 kPa and PaCO₂ 5·4 kPa. The FEV₁ was 2·84 l, FVC 3·17 l, diffusing capacity for carbon monoxide (DCO) 3·14 mmol min⁻¹ kPa⁻¹ (27% predicted) and diffusing coefficient (KCO) 0·75 (48% predicted). The radiographic abnormalities had largely cleared, liver function had returned to normal and he was allowed home.

Cyclophosphamide (150 mg day⁻¹) and prednisolone were continued for 6 months. The prednisolone was reduced by 5 mg every 2 weeks. There was further improvement in lung function over this time, with FEV₁ rising to 4·89 l, FVC 5·91 l, DCO 8·7 mmol min⁻¹ kPa⁻¹ (75% predicted) and KCO 1·16 (75% predicted). There has been no relapse over 18 months on no treatment.

Discussion

The aetiology of BOOP is unknown, but a variety of reports have implicated several chemically-distinct drugs (1,4–8). Bronchiolitis obliterans organizing pneumonia has not been reported previously in association with imipramine or carbamazepine, and evidence here for an aetiological association is not clear. The present patient did not improve on stopping the suspect drugs, as has been seen in some cases associated with acebutalol (6) and gold (7), but such improvement is not consistently seen in drug-related BOOP (4–7). An erythematous rash is described in antibiotic-associated BOOP (4), and interestingly, the present patient’s rash improved after the addition of cyclophosphamide in parallel with his respiratory status. In cases of BOOP it appears wise to discontinue any pre-existing drug treatment.

Initial reports suggested that more than 80% of patients with BOOP showed rapid and complete resolution of the disease on steroids, although relapse could occur as the dose was reduced (2,9). However, patients are now being recognized who demonstrate a more aggressive clinical course with rapidly-progressive disease which is unresponsive to steroids and associated with a high mortality (3). The present patient was given prednisolone at an adequate dose (9,10) for a duration within which clear improvement would be seen in the vast majority of patients (10,11). Instead, he deteriorated alarmingly and the authors considered him to be steroid resistant. In such cases, a number of treatments have been tried including plasmapheresis, immunoglobulins and cyclophosphamide (3,10). These treatments have usually been tried late in the course of the disease and have generally been unsuccessful; however, the present patient showed a dramatic response after the addition of cyclophosphamide. The therapeutic role of cyclophosphamide in this case is unproven because the possibility cannot be dismissed that the improvement was due simply to a further week of prednisolone therapy, and it is not known whether the combination with prednisolone is necessary for efficacy. Definitive recommendations for treatment could only come from controlled study on groups of patients, but the authors’ experience suggests that cyclophosphamide can be given safely in BOOP, and an early therapeutic trial should be considered in patients who fail to respond to steroids.
References