Annals of the Rheumatic Diseases 1991; **50**: 956–958

Bronchiolitis obliterans in systemic lupus erythematosus: beneficial effect of intravenous cyclophosphamide

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Abstract

A 49 year old white woman with systemic lupus erythematosus and bronchiolitis obliterans was treated with prednisone (1 mg/kg daily), which led to a transitory improvement in pulmonary status. Cyclophosphamide was then added—4 mg/kg daily intravenously for five days, then 2 mg/kg daily orally—and this was followed by a dramatic and prolonged improvement.

Pleuropulmonary disease in systemic lupus erythematosus (SLE) is common, occurring in 50 to 70% of patients.[1] Pulmonary complications directly related to SLE are pleural effusion, acute lupus pneumonitis, diffuse interstitial disease, pulmonary hypertension, diaphragmatic dysfunction, atelectasis, and pulmonary haemorrhage. Bronchiolitis obliterans is an exceptional complication of SLE, rarely reported,[2–6] and there are no established guidelines for treatment. There was a prolonged favourable response to cyclophosphamide in this case reported.

Case report

A 49 year old non-smoking woman with a 30 year history of SLE without pulmonary manifestations was admitted in December 1986 for severe dyspnoea with an unproductive cough of acute onset 10 days previously. She had been treated with 10 mg/day prednisone for 20 years and was not taking any other treatment. At admission physical findings were: temperature 38·5°C; pulse 100/min; blood pressure 110/65 mmHg; respiratory rate 30/min. She was dyspnoeic at rest. Pulmonary auscultation was normal. Arterial blood gases were: Pa_{O_2} 8·9 kPa; Pa_{CO_2} 4·26 kPa. Laboratory findings included: haemoglobin 118 g/l; white cell count $3{\cdot}5\times10^9$/l with 58% neutrophils; platelets 240×10^9/l erythrocyte sedimentation rate 50 mm/h; fluorescent antinuclear antibody titre 1/1000; antinative DNA fluorescent antibody titre 1/1280; anti-Ro and anti-ENA were negative; serum complement was low: C3 0·83 g/l (normal >0·94 g/l), C4 0·08 g/l (normal >0·16 g/l), CH50 250 U/ml (normal>400 U/ml). Proteinuria was present (3·35 g/day) linked with nephrotic syndrome. Renal biopsy showed grade 3 focal segmental glomerulonephritis.

Chest radiography showed slight basal interstitial shadowing (fig 1). Results of perfusion lung scanning and echocardiography were normal. Pulmonary function studies and flow-volume curves suggested a mild restrictive problem with small calibre airways affected: forced expiratory flow from 25 to 75% of forced vital capacity (FEF 25–75%) was decreased, the terminal portion of the flow-volume curve was flattened, and carbon monoxide transfer factor (T_LCO) was slightly decreased (table).

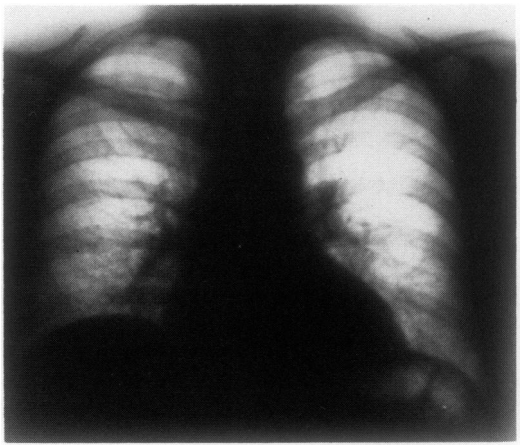

Figure 1 Slight basal interstitial syndrome.

Pulmonary function test results

*Data**	*Dec 1986 Before prednisone treatment 1 mg/kg/day*	*Jan 1987 After prednisone treatment 1 mg/kg/day*	*May 1987 Before cyclophosphamide treatment*	*June 1987 After cyclophosphamide treatment*
FVC (l)	1·96 (73·9)	2·21 (83·3)	1·84 (69·9)	1·89 (77·1)
FEV_1 (l)	1·65 (73·3)	1·80 (80)	1·42 (63·6)	1·52 (73·4)
FEV_1/FVC (%)	84·1	80	77·1	80·4
PEF (l/s)	4·51 (76·5)	5·06 (85·9)	4·54 (77·4)	4·13 (73·2)
FEF 25–75% (l/s)	1·78 (56·1)	2·16 (68·1)	1·28 (40·7)	1·88 (60·8)
Pa_{O_2} (kPa)	8·9	11·3	9·2	10
Pa_{CO_2} (kPa)	4·3	4·9	4·6	4·8
pH	7·50	7·46	7·43	7·47
T_LCO (mmol/min/kPa)	3·75 (50)	ND	4·58 (62)	4·56 (61)
T_LCO/TLC	0·97 (55)	ND	1·32 (76)	1·36 (80)

*Numbers within parentheses are percentages of predicted value.
FVC=forced vital capacity; FEV_1=forced expiratory volume in one second; PEF=peak expiratory flow; FEF 25–75%=forced expiratory flow from 25–75% of FVC; T_LCO=carbon monoxide transfer factor; TLC=total lung capacity.

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Accepted for publication 18 October 1990

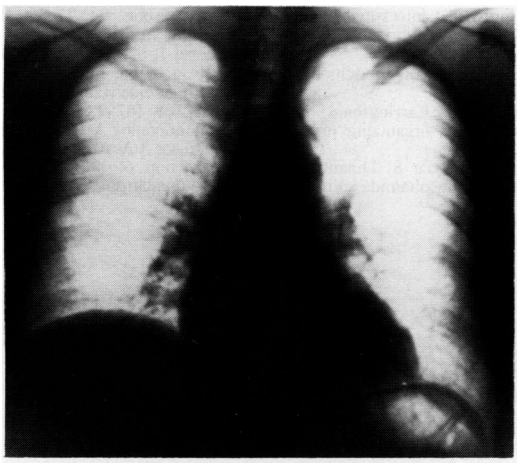

Figure 2 Chest radiograph after treatment.

Bronchoalveolar lavage showed 147×10^9 cells/l with 60% macrophages, 36% lymphocytes, 2% neutrophils, and 1% eosinophils. Bronchoalveolar lavage fluid was sterile. Serological tests for mycoplasma, chlamydia, cytomegalovirus, adenovirus, and respiratory syncytial virus were negative. A diagnosis of bronchiolitis obliterans associated with lupus nephropathy was suspected and treatment started with prednisone 1 mg/kg/daily. Pulmonary status improved initially, dyspnoea disappeared, Pao_2 increased to 11·3 kPa, and chest radiographs became normal. Dyspnoea and hypoxaemia recurred five months later, however (table). No evidence of respiratory tract infection was found. Results of routine laboratory and immunological investigations showed no change. There was no proteinuria. Pulmonary function studies suggested a recurrence of bronchiolitis obliterans (table). Oral prednisone was continued (0·5 mg/kg/daily) and cyclophosphamide was added: an intravenous bolus of cyclophosphamide 4 mg/kg/daily for five days, followed by oral cyclophosphamide 2 mg/kg/daily.

Two days after this treatment was started the patient's clinical condition improved dramatically, accompanied by an improvement in Pao_2 (table). Oral cyclophosphamide treatment was stopped after five months because of neutropenia. At the time of writing, nearly three years after the onset of pulmonary symptoms, the patient is asymptomatic and still receiving 15 mg/day prednisone. Chest radiography results are normal, Pao_2 and T_LCO are normal (95% of predicted value) (fig 2).

Discussion

Bronchiolitis obliterans is a lesion which results when damage to small calibre conducting airways is repaired by proliferation of granulation tissue. The extension of granulation tissue into alveoli is often described as 'organising pneumonia'.[7] Histological proof is required for the diagnosis, but open lung biopsy is invasive and transbronchial lung biopsy is not recommended because of the small specimens which it yields and the patchy nature of the disease.[8] In this report we obtained no pulmonary histological proof. Nevertheless, we consider that pulmonary symptomatology was probably due to bronchiolitis obliterans as clinical symptoms, radiological and pulmonary function abnormalities, as well as the initial improvement due to prednisone were compatible with such a diagnosis in the light of previous reports.[6–8] The clinical onset of bronchiolitis obliterans is acute. Fever, cough, and dyspnoea are the commonest presenting complaints. Radiological signs are variable, but bilateral, patchy, ground glass, or alveolar opacities are commonly seen. Pulmonary function studies show airflow obstruction or volume restriction, or both. Hypoxaemia is a constant finding and T_LCO may be abnormal in 70% of patients.

Bronchiolitis obliterans is one of a number of several pulmonary lesions seen in connective tissue disorders. It has been reported in rheumatoid arthritis—mainly in association with D-penicillamine treatment.[9 10] In SLE isolated mild abnormalities of small calibre airways have been described in pulmonary function studies,[11] but these are of no clinical significance. In contrast, lupus bronchiolitis with clinical manifestations is quite exceptional. Bronchiolitis obliterans has also been reported in adults as a result of infection or exposure to toxic fumes.[7] In our patient bronchiolitis was probably due to SLE as there was no toxic exposure, bacteriological samples and serological tests were negative, and the pulmonary lesion was concomitant with the onset of her lupus nephropathy. The lymphocytosis and normal neutrophil count in bronchoalveolar lavage did not indicate any infectious cause or the presence of pulmonary fibrosis.

Epler *et al* have emphasised the efficacy of corticosteroids in treating bronchiolitis obliterans.[8] In their cases, however, patients with connective tissue diseases had a poor prognosis, though death was not always due to lung disease. In SLE corticosteroids are effective but dependence is common.[3 4] One case of lupus bronchiolitis unsuccessfully treated with cyclophosphamide has been reported, but no details were given about dose or management.[4] In our patient corticosteroids had to be combined with cyclophosphamide to achieve long term improvement. The beneficial effect of intravenous cyclophosphamide treatment has already been reported in a patient with D-penicillamine associated bronchiolitis obliterans in association with rheumatoid arthritis.[9] We consider that bolus cyclophosphamide treatment, in addition to oral prednisone, may be effective in the treatment of this unusual condition.

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