

Obliterative bronchiolitis in rheumatoid arthritis

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SUMMARY Two patients with rheumatoid arthritis who developed obliterative bronchiolitis are described. Both patients had received penicillamine. The first patient died in respiratory failure 4 months after the onset of her breathlessness and the diagnosis was confirmed at post-mortem. The second patient was diagnosed with appropriate lung function tests and has been started on azathioprine. Although she is still disabled by breathlessness 12 months after presentation, her condition has stabilised.

Rheumatoid arthritis may be associated with a number of pulmonary complications including pleural effusions, rheumatoid lung nodules, fibrosing alveolitis, bronchiectasis, and airways obstruction.¹ Obliterative bronchiolitis, which occurs in adults most frequently following inhalation of toxic fumes,² has recently been reported to occur in patients with rheumatoid arthritis,³ possibly following treatment with penicillamine.^{4,5} In this report we describe 2 further cases of obliterative bronchiolitis in patients with rheumatoid disease both of whom had received penicillamine treatment.

Case reports

CASE 1

A 63-year-old woman with a 5-year history of erosive but seronegative rheumatoid arthritis was admitted to hospital in May 1977 complaining of rapidly worsening dyspnoea of recent onset and an unproductive cough. There was no history of inhalation of toxic fumes or chronic respiratory disorder, and the patient had never smoked.

She had had rheumatoid arthritis since 1972 and for the first 4 years of the disease was treated with a variety of nonsteroidal anti-inflammatory drugs, but in February 1976 because of continuing active disease she was successfully started on penicillamine in a dosage that never exceeded 375 mg daily.

In February 1977 she underwent a Freeman knee arthroplasty under general anaesthesia. In May she complained of dyspnoea at rest. On examination there was neither clubbing nor cyanosis. She had a parasternal heave with an accentuation of the pulmonary component of the second sound but normal

venous pressure. Coarse crepitations were heard throughout both lung fields and a variable inspiratory and expiratory wheeze. There was nothing to suggest a deep venous thrombosis.

Initial investigations included a normal chest x-ray and electrocardiogram (ECG) and a total white cell count of $13.7 \times 10^9/l$, erythrocyte sedimentation rate (ESR) 25 mm/h, IgM RF (Hyland latex test) negative, antinuclear factor (ANF) negative, and there was no bacteriological or serological evidence to suggest respiratory infection. A ventilation/perfusion scan suggested underperfusion in the lower zone of the left lung. A diagnosis of pulmonary embolism was made and she was started on warfarin, but subsequent pulmonary angiography was entirely normal. Lung function studies (Table 1) showed an obstructive airways pattern with a slightly reduced transfer factor. A transbronchial biopsy showed no evidence of parenchymal lung disease, and the wedge pressure was normal at Swan-Ganz catheterisation.

After several weeks on a combination of anti-coagulants, diuretics, and various bronchodilators she failed to improve and was speculatively started on prednisolone 5 mg b.d. Azathioprine was briefly introduced, but it had to be rapidly discontinued because of severe oral ulceration. Despite all these measures she steadily deteriorated and died in respiratory failure 5 months after presentation.

At necropsy both lungs were voluminous and overinflated, deflating with difficulty on external pressure. The only macroscopic abnormalities were minimal bronchiectasis of the right middle lobe bronchus, with mild lobular consolidation of the left upper lobe. There was no emphysema. Microscopically changes were seen throughout the lungs typical of a bronchiolitis obliterans. Bronchioles were occluded by mucus, chronic inflammatory cells, and epithelial debris, their walls being thickened by granulation

Accepted for publication 18 August 1981.

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Table 1 Results of lung function studies

	Case 1		Case 2			
	Observed	% Predicted	At presentation Aug. 1980		July 1981 on azathioprine	
			Observed	% Predicted	Observed	% Predicted
PEFR (l/min)	150	45	280	73	240	63
FEV ₁ (l)	0.6	31	1.2	52	1.15	49
FVC (l)	0.65	29	2.15	68	2.35	74
VC (l)	0.94	41	2.51	79	2.61	83
FEV ₁ /FVC (%)	92	—	56	72	49	63
MMEFR (l/s)	—	—	0.73	20	—	—
TLC (l)	2.57	65	5	100	4.75	95
RV (l)	1.63	107	2.49	135	2.14	115
FRC (l)	1.69	79	3.42	130	2.64	108
Transfer factor for						
CO (ml/min/mmHg)	8.65	43	13	42	15	63
Kco			4.8	96	5.17	103
Static lung compliance				Normal		

tissue and a moderate, chronic inflammatory infiltrate, predominantly lymphocytic but also containing small numbers of plasma cells and eosinophils. These changes involved the mucosa and muscle coats, occasionally spreading to the peribronchial tissues (Fig. 1). In some smaller bronchioles the mucosa was ulcerated, with the formation of granulation tissue polyps. The alveolar ducts and alveoli were not involved. No features suggestive of either chronic bronchitis or asthma were present. There was no evidence of pulmonary embolism or primary pulmonary hypertension, and the heart was normal.

CASE 2

A 56-year-old woman was admitted to hospital in

August 1980 with an 8-month history of cough and wheezing and a 4-month period of rapidly worsening dyspnoea.

She had suffered from rheumatoid arthritis since 1969, with the development of Sjögren's syndrome in 1977. She was treated with low-dose prednisolone, a variety of nonsteroidal anti-inflammatory drugs, and a short course of hydroxychloroquine. In September 1977 she was started on penicillamine 125 mg daily, the dose being progressively increased to 375 mg daily. By April 1978 the disease had remitted sufficiently for the prednisolone to be withdrawn completely for the first time. Treatment was complicated throughout by recurrent episodes of thrombocytopenia, but the dose of penicillamine was even-

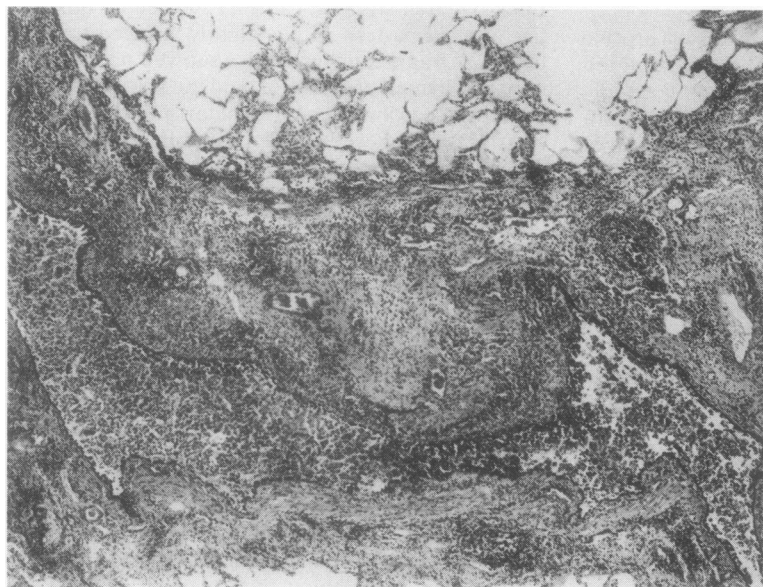


Fig. 1 Small bronchus filled with inflammatory and epithelial debris. The wall is replaced by granulation tissue extending into the peribronchial tissues. (Haematoxylin and eosin, $\times 1.3$).

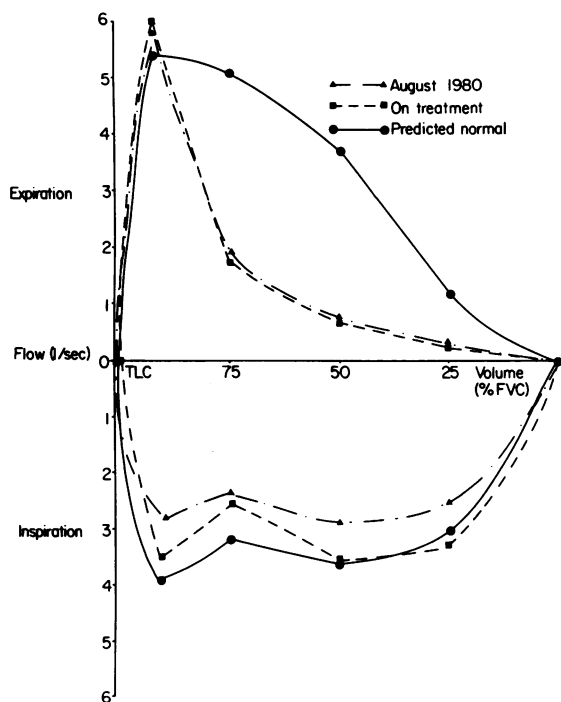


Fig. 2 Flow volume loops from case 2. Flow rate is plotted on the ordinate (l/s) and volume, as a percentage of the forced vital capacity (FVC) on the abscissa. \blacktriangle — \blacktriangle at the time of presentation—August 1980. \blacksquare — \blacksquare on azathioprine 150 mg daily—July 1981. \bullet — \bullet predicted normal.*

tually stabilised in 1979 at 50 mg daily. There was no history of previous respiratory tract disease or exposure to toxic fumes before the onset of her respiratory symptoms. She was a nonsmoker.

On admission she was dyspnoeic at rest. There were bilateral coarse basal crepitations, and a midinspiratory squeak was audible throughout both lung fields.

Investigations showed a mild hypochromic microcytic anaemia at 10.4 g/dl, total white cell count $8.4 \times 10^9/l$, ESR 75 mm/h, IgM RF (differential agglutination titre) positive 1/32, ANF negative. The

chest x-ray showed no abnormality apart from hyperinflation, and her arterial blood gases were PO_2 10.1 kPa and PCO_2 9.2 kPa. Pulmonary function tests are shown in Table 1 and her flow volume measurements in Table 2 and Fig. 1. These show severe airways obstruction at low lung volumes with normal lung compliance and a normal K_{CO} . There was no improvement after a bronchodilator.

Her penicillamine was stopped and she was started on prednisolone 40 mg daily, which after 14 days produced no improvement. The steroid was subsequently reduced and the patient put on azathioprine 50 mg b.d. Her respiratory function continued to deteriorate until the azathioprine was increased to 150 mg daily. On this higher dose her effort tolerance improved and her lung function studies have stopped deteriorating (Table 2 and Fig. 2).

Discussion

These 2 patients with rheumatoid arthritis developed generalised small airways obstruction. The first was diagnosed only at necropsy; the second was diagnosed with appropriate lung function testing. She has been started on azathioprine and her disease appears to be stabilising. Both patients had received penicillamine.

The diagnosis of the condition requires elimination of more common conditions such as multiple pulmonary emboli, large airways obstruction, parenchymal lung disease, and pulmonary oedema. Clinically, rapidly progressing dyspnoea, unproductive cough, basal crepitations, and a very distinctive midinspiratory squeak,³ which was mistaken in our first case for a wheeze, are the most informative features. The duration and activity of the rheumatoid arthritis do not appear to be of any clinical significance. The chest x-ray is usually normal or shows hyperinflation only. However, appropriate lung function tests enable the diagnosis to be made quickly and confidently. These show the characteristic pattern of airways obstruction at low lung volumes, with normal compliance excluding emphysema, and normal or only slightly reduced transfer factor. Transbronchial lung biopsy is usually unhelpful in diagnosing this condition, although it may be necessary to exclude parenchymal disease.

Table 2 Flow volume measurements on case 2 showing low flow rates on expiration at low lung volumes

	Expiration			Inspiration		
	Predicted	Observed Aug. 1980	Observed July 1981	Predicted	Observed Aug. 1980	Observed July 1981
PFR	5.4	5.82	4.8	3.9	2.91	3.0
Flow at 75% FVC	5.1	1.82	1.6	3.2	2.37	2.3
Flow at 50% FVC	3.7	0.73	0.9	3.6	2.91	2.8
Flow at 25% FVC	1.2	0.36	0.4	3.1	2.64	2.9

Evidence implicating penicillamine as a causal agent in this rare but serious complication of rheumatoid arthritis is conflicting. Of the 12 cases that have previously been reported from various centres 9 received penicillamine.³⁻⁶ Against this must be considered the relative paucity of cases among large numbers of patients treated with this useful drug.⁷ We recommend that all patients receiving it who develop unexplained respiratory symptoms be carefully examined with obliterative bronchiolitis in mind, and have appropriate lung function tests if necessary.

Obliterative bronchiolitis does not respond to corticosteroids and has an invariably poor, if not fatal outcome, within a few months of its diagnosis. It is of some interest that our second patient has had an improvement in her exercise tolerance since beginning azathioprine and her lung function studies have stabilised.

We thank Dr M. H. Pritchard and Dr J. Jessop for permission to report patients under their care.

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