Clinicopathological study of migratory lung infiltrates

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Abstract

Clinical features and the histological appearances of transbronchial lung biopsy specimens were investigated in 11 patients with migratory infiltrates on the chest radiograph. Serum circulating immune complexes were increased at the time that infiltrates were present in all patients and the levels returned to normal as patients recovered clinically and radiologically. The Mantoux test response was negative in most patients. Fifty serial sections were obtained from each paraffin embedded biopsy specimen block and every 10th section was stained (step sectioning) with haematoxylin and eosin. Six patients (group 1) did not have eosinophilic infiltration; four of these had granulation tissue plugs within respiratory bronchioles when the tissue was examined by step sectioning. All had organising pneumonia and interstitial inflammation in the setting of a clinical picture consistent with bronchiolitis obliterans organising pneumonia. In two cases IgG had been deposited in intra-alveolar macrophages. Biopsy specimens in five patients (group 2) showed eosinophilic infiltration; four patients had chronic eosinophilic pneumonia and one the Churg-Strauss syndrome. Step sectioning of transbronchial biopsy specimens in patients with migratory pulmonary infiltrates is useful and may support the diagnosis of bronchiolitis obliterans organising pneumonia.

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Patients with unexplained migratory infiltrates on serial chest radiographs are rare and few systematic clinicopathological studies have been carried out in such patients. Such migratory infiltrates are generally believed to represent simple pulmonary eosinophilia (Loeffler's syndrome),[1 2] though bronchiolitis obliterans organising pneumonia may present in this way.[3 4]

This study was undertaken to assess the clinical and histopathological features of tissue obtained from transbronchial biopsy in patients with migratory infiltrates. We also investigated the value of step sectioning of these biopsy specimens.

Methods

Eleven patients with migratory chest infiltrates presented from 1 January 1980 to 31 December 1989. We reviewed their clinical records and chest radiographs retrospectively and re-examined their original paraffin embedded

Table 1 Clinical features of group 1

Patient No:	*1*	*2*	*3*	*4*	*5*	*6*
Age (y)	61	73	79	71	64	72
Sex	F	M	M	F	F	M
Underlying disease	(−)	(−)	Aspergilloma bronchiectasis	(−)	(−)	(−)
Symptoms	Cough fever dyspnoea	Cough fever	Cough fever sputum	Fever malaise	Cough fever dyspnoea	Cough dyspnoea
White blood cell count/($\times 10^9$/l)	8·6	8·2	10·1	9·9	10·7	7·5
Eosinophils (%)	1	2	1	2	3	5
ESR (mm in 1 hour)	127	146	124	120	128	68
Mantoux test (mm)						
Erythema	0	0	0	0	0	0
Induration	4 × 7	11 × 10	0	0	0	3 × 5
CIC(%)*						
Before treatment	80	87	80	88	100	40
After treatment	NE	0	NE	0	0	0
Antipathogen antibody	(−)	Legionella	(−)	Mycoplasma	(−)	(−)
FVC (% predicted)	89	NE	30	75	67	52
FEV_1 (% predicted)	81	NE	33	77	53	58
$Pao_2/Paco_2$ (room air; mm Hg)	96/36	70/30	84/31	65/31	55/34	70/45
Antibiotics	(−)	Erythromycin	Aztreonam imipenem	Minocycline	(−)	Erythromycin
Steroid (mg)	PSL (30)	PSL (30)	M-PSL (1000)	(−)	PSL (20)	(−)
Outcome	Improved	Improved	Died	Improved	Improved	Improved

*Normal 0–20%.
ESR—erythrocyte sedimentation rate; CIC—circulating immune complex; NE—not examined; FVC—forced vital capacity; FEV_1 forced expiratory volume in one second; Pao_2—arterial oxygen tension; $Paco_2$—arterial carbon dioxide tension; PSL—prednisolone; M—PSL-methylprednisolone.
Conversion to SI units: 1 mm Hg = 0·133 kPa.

Table 2 Clinical features of group 2

Patient No:	*7*	*8*	*9*	*10*	*11*
Age (y)	68	55	81	68	51
Sex	M	F	F	F	M
Underlying disease	Hypertension	(-)	Hypertension diabetes mellitus	(-)	Sinusitis
Symptoms	Fever cough	Cough sputum fever	dyspnoea	Cough malaise	Cough sputum
White blood cell count ($\times 10^9$/l)	6·5	9·4	11·0	7·5	7·3
Eosinophils (%)	11	19	31	10	44
ESR (mm in 1 hour)	105	142	58	161	34
Mantoux test (mm)					
Erythema	0	8 × 15	0	0	2 × 2
Induration	3 × 2	25 × 23	3 × 3	2 × 3	12 × 10
CIC (%)*					
Before treatment	NE	100	99	98	24
After treatment	17	0	23	3	0
IgE (IU/ml)†	350	600	7700	250	1300
Skin test responses	Candida (+)	Candida (±)	Candida (+) Aspergillus (±)	(−)	(−)
FVC (% predicted)	85	50	39	100	72
FEV_1 (% predicted)	98	67	40	79	55
$Pao_2/Paco_2$ (room air, mm Hg)	69/40	86/38	81/35	70/40	61/40
Steroid (mg)	PSL (20)	(-)	(-)	PSL(20)	PSL(20)
Outcome	Improved	Improved	Improved	Improved	Improved

*Normal 0–20%.
†Normal 0–250 IU/ml.
Abbreviations and conversion factor as in table 1.

transbronchial biopsy material by step sectioning.

Serum circulating immune complex levels had been measured by the polyethylene glycol precipitation-complement consumption test.[5]

Three to five transbronchial biopsy specimens were taken from the area that appeared to be most abnormal on the chest radiograph, fixed in 10% buffered formalin, and embedded in paraffin. We studied one or two sections from each specimen in a routine manner and then prepared 50 serial sections from each paraffin embedded specimen block, staining every 10th section with haematoxylin and eosin (step sectioning). Each section was then studied in detail with respect to bronchiolitis obliterans, alveolar organisation, alveolar foam cells, interstitial inflammation, alveolar eosinophils, interstitial eosinophils, and pulmonary vasculitis. Elastic van Gieson staining was performed on several sections to allow the bronchioles to be visualised better.

Immunohistochemical staining was performed with antibodies against human IgG, IgA, IgM, C3, and C4.

Results

CLINICAL FEATURES

The clinical characteristics of the patients and their pulmonary function are summarised in tables 1 and 2.

The patients were divided into two groups, based on the presence or absence of eosinophilic infiltration in the biopsied pulmonary tissue.

Group 1 (no eosinophilic infiltration) consisted of three men and three women, all of whom presented with an influenza like illness, with cough and fever; three had dyspnoea.

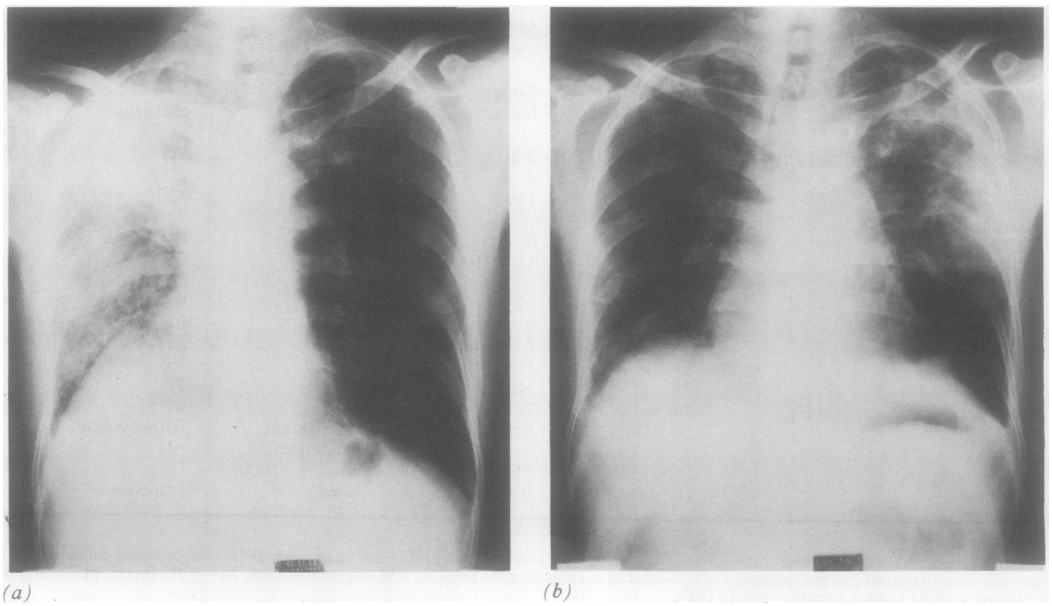

Figure 1 Patient 2: Chest radiographs showing (a) mixed alveolar and interstitial infiltrates and pleural effusion in the right lung field and (b) infiltrates in the left upper and middle lung fields with a regressing infiltrate in the right lung field.

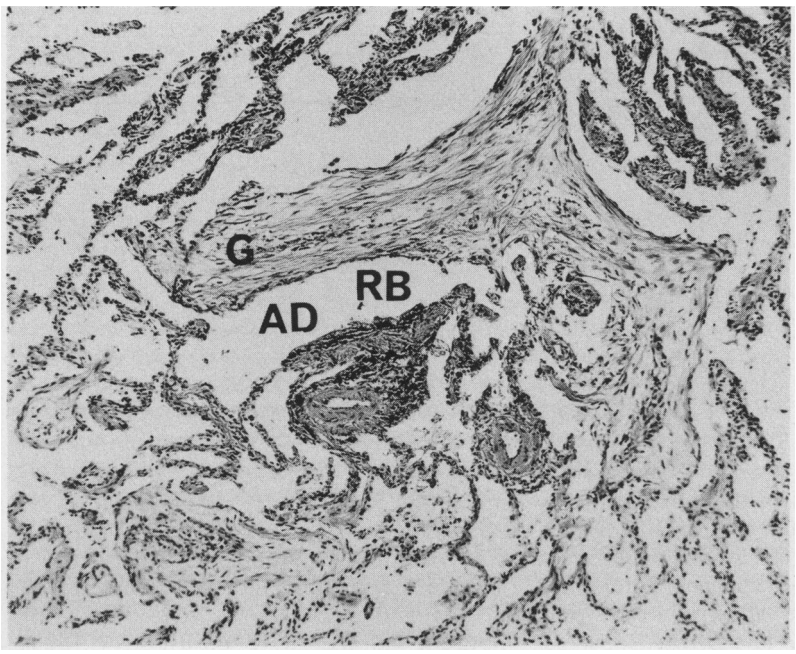

Figure 2 Patient 1: Granulation tissue (G) extending from a respiratory bronchiole (RB) into an alveolar duct (AD). Adjacent alveolar ducts are also affected. (Haematoxylin and eosin; transbronchial biopsy specimen examined by step sectioning.)

They had a considerably raised erythrocyte sedimentation rate and slight leucocytosis, and circulating immune complex levels were increased but returned to normal after treatment. Mantoux test responses were negative in all but one patient. Physiological studies tended to show a restrictive pattern. All were treated initially with cephalosporins without success. The mycoplasma antibody titre was raised in patient 4, who improved rapidly after minocycline treatment. Patient 2 had an initial indirect fluorescent antibody titre for legionnaires' disease of 1:64. Despite some initial improvement with erythromycin he continued to have symptoms and the shadowing on the chest radiograph increased. This patient and three of the other patients improved rapidly both clinically and radiologically within a few days of starting prednisolone treatment. No relapses occurred as the prednisolone dose was tapered. Patient 3 seemed to improve spontaneously, though the chest radiograph deteriorated. He did not improve with high dose methylprednisolone treatment and died two weeks later. Sputum culture and necropsy revealed *Pseudomonas aeruginosa* pneumonia.

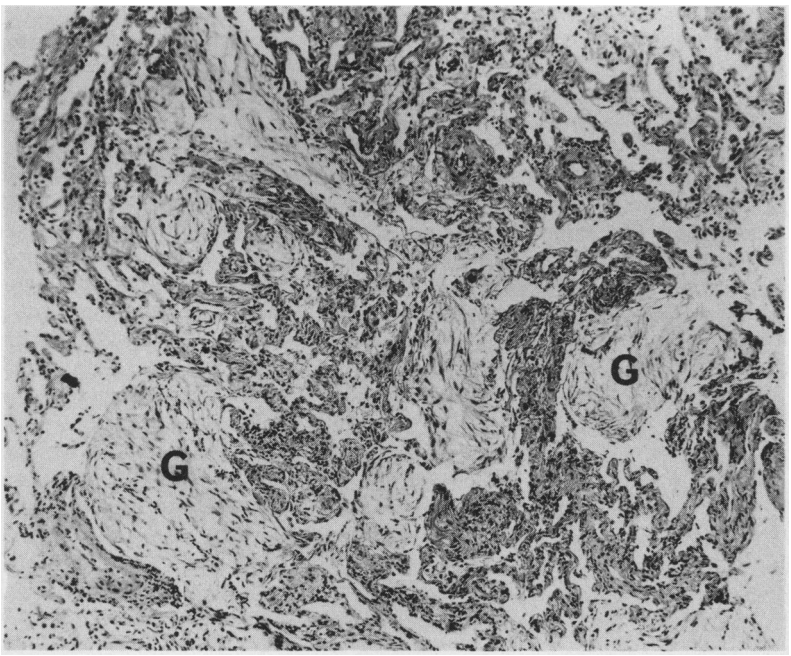

Figure 3 Patient 2: Polypoid masses of granulation tissue (G) filling the lumen of alveolar ducts and extending into alveoli (organising pneumonia). Adjacent alveolar walls are infiltrated by mononuclear cells. (Haematoxylin and eosin; transbronchial biopsy specimen examined by step sectioning.)

Group 2 (with eosinophilic infiltration) consisted of two men and three women. Cough and fever were prominent. Patient 11 had a two year history of asthma, erythema, and a peripheral nerve palsy; skin biopsy showed small artery vasculitis. All patients had symptoms for one to six weeks before referral to hospital. Peripheral blood eosinophilia (10–44%) was seen in all. The erythrocyte sedimentation rate was over 100 mm in the first hour in three patients. Circulating immune complexes were increased initially but returned to normal as the patient improved spontaneously or with treatment. The Mantoux test response was negative in three patients. None had been taking any drug and no parasites were found in sputum or lung tissue. Skin tests for fungi gave a positive result in three patients but this was not thought to be a specific finding. Pulmonary function testing showed a restrictive defect in three cases. A rapid clinical response to prednisolone, with complete resolution of symptoms and a return of the chest radiograph to normal, was seen within two weeks in three patients. Two patients improved spontaneously.

CHEST RADIOGRAPHS

In all patients infiltrates appeared at one site while they were regressing in others both before and during treatment. Radiologically, the infiltrates were patchy and non-segmental with mixed alveolar and interstitial characteristics. Pleural effusion was seen only in patient 2. Neither pulmonary cavitation nor lymphadenopathy was seen in any patient. There was no difference in the pattern or distribution of the radiographic opacities between groups 1 and 2 (fig 1).

HISTOLOGY

The histopathological profiles seen on step sectioning are summarised in table 3 and illustrated in figures 2–6. In group 1 granulation tissue plugging of alveolar ducts (intra-alveolar organisation) was common in each case. Plugging of respiratory bronchioles by granulation tissue (bronchiolitis obliterans) was seen in specimens from four of the six patients examined by step sectioning. In three of these patients bronchiolitis obliterans had not been seen in the original routine sections. Elastic van Gieson stains provided additional evidence that bronchioles were plugged but all

Table 3 Summary of histological findings

Patient No	Bronchiolitis obliterans	Intra-alveolar organisation	Intra-alveolar foam cells	Interstitial inflammation	Intra-alveolar eosinophils	Interstitial eosinophils	Pulmonary vasculitis
Group 1							
1	+*	+	+	+	−	−	−
2	+	+	+*	+	−	−	−
3	+*	+	+	+	−	−	−
4	+*	+	+*	+	−	−	−
5	−	+	+	+	−	−	−
6	−	+*	+*	+	−	−	−
Group 2							
7	−	+	+	+	+	+	−
8	−	+	+*	+	−	+	−
9	−	−	+	+	+	+	−
10	−	+	+	+	+*	+*	−
11	−	−	+*	+	+	+	−

*Additional findings from step sectioning.

of the bronchioles seen in these four patients seemed to be respiratory bronchioles; we could not find plugging in terminal bronchioles. Alveolar foam cells and interstitial inflammation composed of lymphocytes and plasma cells were seen in all patients.

In group 2 alveolar and interstitial eosinophils were common. No patient had bronchiolitis obliterans. An eosinophilic microabscess was seen in patient 10. Pulmonary vasculitis was not seen.

Immunohistochemical staining showed IgG deposition in the alveolar macrophages in patients 2 and 3 (group 1).

FINAL DIAGNOSIS

The six patients in group 1 had clinicopathological findings consistent with bronchiolitis obliterans organising pneumonia. In patient 4 this was believed to be due to *Mycoplasma pneumoniae* pneumonia and in patient 2 to *Legionella pneumophila* pneumonia. In the other four cases no known cause of pulmonary disease was found. No patient had a history of toxic fume inhalation, aspiration of gastric fluids, or lung transplantation. Signs and symptoms of underlying connective tissue disease could not be found. Serological tests for infectious agents (including legionella, mycoplasma, and chlamydia) gave negative results. Sputum cultures were positive for *Haemophilus influenza* and *Klebsiella* sp in patient 3 and, although moderate bronchiectatic changes were seen in his left lung, the infiltrates migrated in the right upper zone, which had originally appeared to be normal on the chest radiograph. Step sectioning of a transbronchial biopsy specimen taken from that area showed no neutrophil infiltration. Necropsy revealed *Pseudomonas aeruginosa* pneumonia throughout the left lung and in the right lower lobe. The right upper lobe was essentially normal, however, and bronchiolotis obliterans could no longer be found.

In group 2 patient 11 was diagnosed as having the Churg-Strauss syndrome. The other four patients had no pre-existing atopic disease and no relevant drug history, and no parasites were found despite a careful search. They had symptoms for more than four weeks and were considered to have chronic eosinophilic pneumonia.[6]

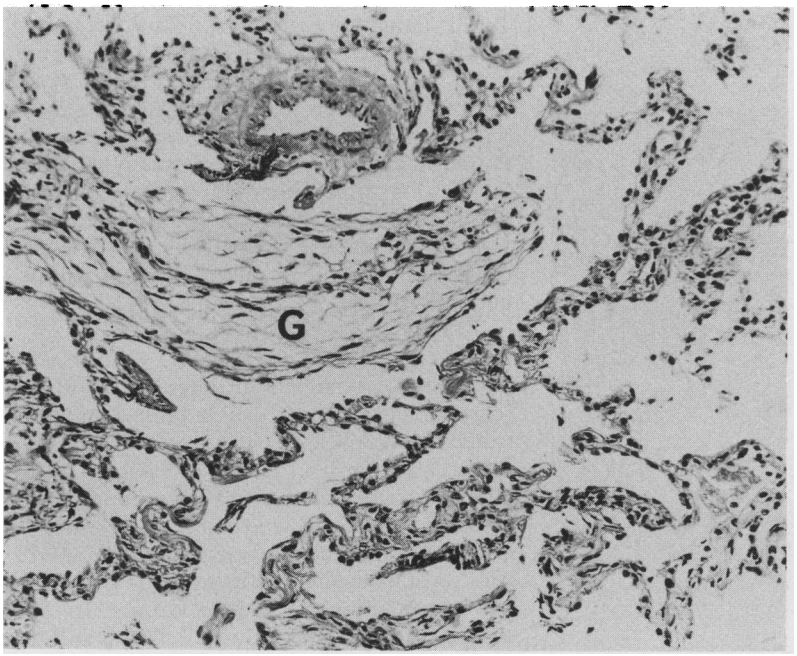

Figure 4 Patient 3: Granulation tissue (G) extending into an alveolus (organising pneumonia). (Haematoxylin and eosin; transbronchial biopsy specimen examined by step sectioning.)

Disussion

In this clinicopathological study of 11 patients with migratory lung infiltrates, six had findings consistent with bronchiolitis obliterans organising pneumonia; four had chronic eosinophilic pneumonia, and one the Churg-Strauss syndrome. Immunological abnormalities were found in both groups, suggesting that an immune mechanism may cause these migrating pulmonary infiltrates. Combining step sectioning of transbronchial biopsy specimens with clinical findings in the setting of characteristic migrating pulmonary infiltrates allowed us to make the diagnosis of bronchiolitis obliterans organising pneumonia.

In a review of 119 cases of chronic eosinophilic pneumonia peripheral infiltrates were the most common radiographic abnormality.[6] Jedelinic *et al*[6] also described four cases of migratory infiltrates. Pulmonary eosinophilia[2] is seen in Loeffler's syndrome, chronic eosinophilic pneumonia and the Churg-Strauss syndrome; migration of pulmonary infiltrates has

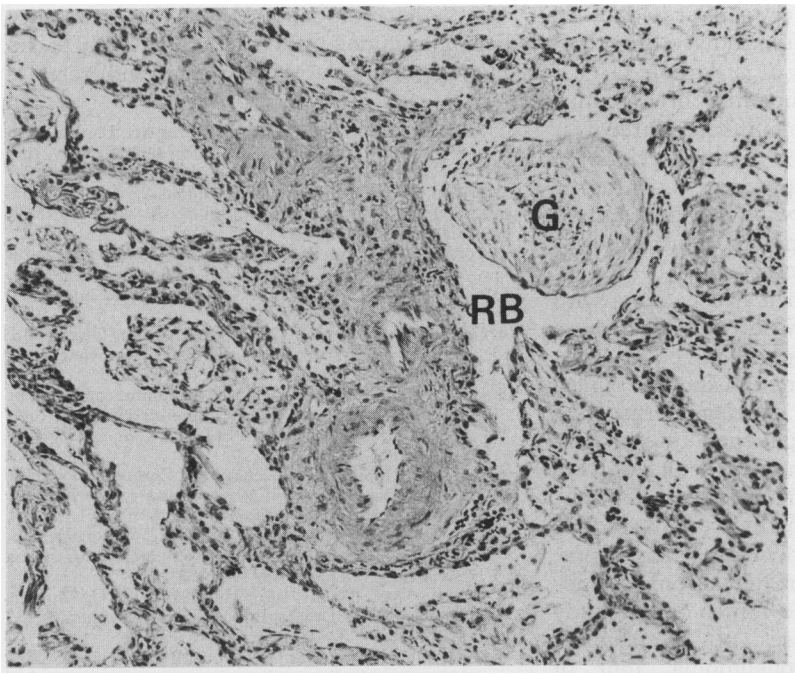

Figure 5 Patient 4: Polypoid granulation tissue (G) containing nuclear debris in the centre in the lumen of a respiratory bronchiole (RB). The surface of the organisation tissue shows re-epithelialisation. (Haematoxylin and eosin; transbronchial biopsy specimen examined by step sectioning.)

been seen most commonly in patients with Loeffler's syndrome.[1]

Six of our patients with migratory pulmonary infiltrates did not have peripheral blood eosinophilia or eosinophils in biopsied lung tissue. These patients had a subacute clinical course with influenza like symptoms, a raised erythrocyte sedimentation rate, and slight leucocytosis, and five had a restrictive lung defect. These patients did not respond to cephalosporins but improved rapidly with prednisolone. These clinical characteristics were consistent with bronchiolitis obliterans organising pneumonia as reported by Epler *et al*[7] and, two years earlier, by Davison *et al*,[8] who called the condition cryptogenic organising pneumonitis.

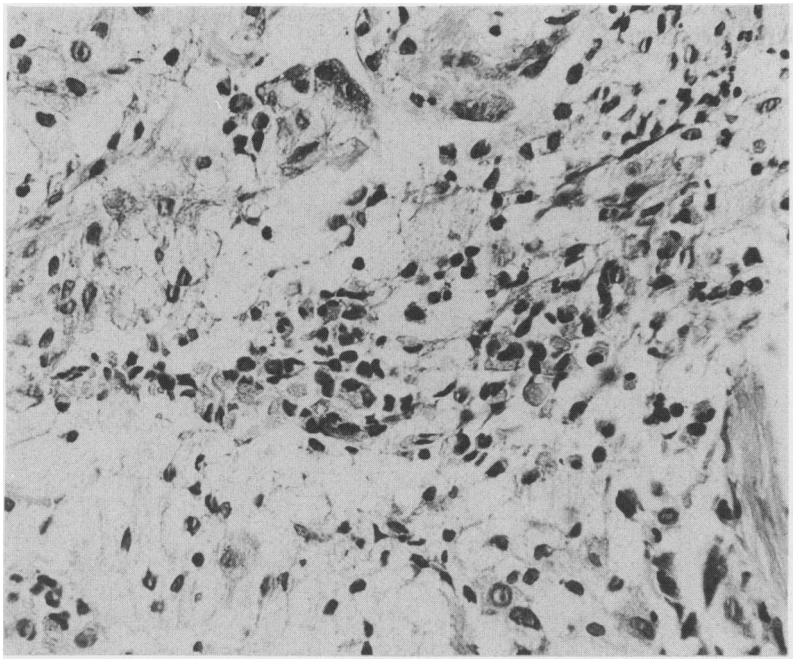

Figure 6 Patient 10: Intraalveolar eosinophilic infiltration intermingled with foam cells. (Haematoxylin and eosin; transbronchial biopsy specimen examined by step sectioning.)

Since 1985 there have been many clinical reports of patients with bronchiolitis obliterans organising pneumonia who had a radiographic pattern of bilateral, patchy, ground glass or alveolar opacities.[7 9-11] Some have had migratory infiltrates.[3 4] Cordier *et al*[3] described three characteristic clinical and radiographic profiles in 16 patients with bronchiolitis obliterans organising pneumonia. Four patients had patchy migratory pneumonia and clinical features that were similar to those in our patients. In previous reports[7 8] migratory infiltrates were seen during relapse, but in our patients the infiltrates migrated before and during treatment and no patient relapsed.

When examined by step sectioning transbronchial biopsy specimens showed bronchiolitis obliterans in four of the six patients. Intra-alveolar organisation and interstitial inflammation were seen in all patients. The granulation tissue in small airways extended into the alveoli, signifying organising pneumonia. Although individually these pathological findings may not be specific, collectively they are characteristic of bronchiolitis obliterans organising pneumonia.[10 12] We believe it likely therefore that the patients in group 1 had bronchiolitis obliterans organising pneumonia.

Specimens obtained by transbronchial biopsy are often considered inadequate for studying bronchioles and for this reason open lung biopsy has been recommended for the definitive diagnosis of bronchiolitis obliterans organising pneumonia.[7] This procedure carries a higher morbidity, however. Only one or two sections of a transbronchial biopsy specimen undergo routine histological examination in some pathology laboratories. We were able to detect bronchiolitis obliterans organising pneumonia and interstitial inflammation more clearly by examining transbronchial biopsy specimens by step sectioning. Myers *et al*[13] reviewed 30 cases of suspected bronchiolitis obliterans organising pneumonia and reported that the diagnosis can be established reliably by transbronchial biopsy provided that related clinical, laboratory, and radiographic findings are evaluated carefully and correlated with the pathological findings. Bartter *et al*[14] showed that non-thoracotomy biopsy material showing bronchiolitis obliterans organising pneumonia may be adequate to guide treatment and allow the clinicians to avoid the expense and potential morbidity associated with open lung biopsy.

We described four patients with idiopathic bronchiolitis obliterans organising pneumonia, in one case due to mycoplasma infection and in one related to legionella infection. Postinfectious bronchiolitis obliterans is usually seen in children and is rare in adults. Few of these cases have been confirmed histologically.[15] Bronchiolitis obliterans due to *Mycoplasma pneumoniae* has been reported,[16 17] though migratory infiltrates were not described. The clinical

course of patient 2 was very similar to that of a patient previously reported to have bronchiolitis obliterans caused by *L pneumophilia*.[18] Of 50 patients with idiopathic bronchiolitis obliterans organising pneumonia, three responded to tetracycline or erythromycin.[7] We believe that an infectious agent, such as *M pneumoniae* or *L pneumophila*, may have caused some cases of "idiopathic" bronchiolitis obliterans organising pneumonia.

Bartter *et al*[14] described five patients with peripheral pulmonary infiltrates similar to those described for chronic eosinophilic pneumonia. Histopathological examination showed typical changes of bronchiolitis obliterans organising pneumonia in all of the patients. Two of their patients had changes consistent with resolving chronic eosinophilic pneumonia. They emphasised that idiopathic bronchiolitis obliterans organising pneumonia may represent the evolution of untreated chronic eosinophilic pneumonia. In the course of our study we discovered six cases of bronchiolitis obliterans organising pneumonia, four of chronic eosinophilic pneumonia, and one of the Churg-Strauss syndrome. We also identified several features, besides migratory infiltrates, that may be seen in both bronchiolitis obliterans organising pneumonia and chronic eosinophilic pneumonia. These features were an influenza like syndrome, a raised erythrocyte sedimentation rate, leucocytosis, a restrictive pattern of lung function values, and a good response to corticosteroids. Increased serum circulating immune complexes and a negative response to the Mantoux test were seen commonly in both groups. Allergic factors are believed to be important in the pathogenesis of chronic eosinophilic pneumonia.[2 6] Immunoglobulins G, M, and A were found both in the bronchial walls and in the pulmonary interstitium in chronic eosinophilic pneumonia.[19] Two of our patients with bronchiolitis obliterans organising pneumonia had IgG deposition in intra-alveolar macrophages. We believe that our data support the possibility that an immunological reaction is central to the aetiology of migratory pulmonary infiltrates.

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