Interrelationship of chronic eosinophilic pneumonia, bronchiolitis obliterans, and rheumatoid disease: a hypothesis

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SUMMARY Three patients with histologically proven bronchiolitis obliterans are presented, two of whom had rheumatoid disease. All three patients had, in addition, clinical and radiological evidence of chronic eosinophilic pneumonia; open lung biopsy in two showed coexistent features of chronic eosinophilic pneumonia and bronchiolitis obliterans. The association of both rheumatoid disease and chronic eosinophilic pneumonia with bronchiolitis obliterans in these patients may simply be coincidental, but the striking similarities between the cases suggest that a real interrelationship of these disease entities may exist.

The catalogue of respiratory complications of rheumatoid disease has recently been extended to include airways obstruction. Although airways disease in these patients is usually mild, a rapidly progressive form of bronchiolitis obliterans has been described in five patients with rheumatoid disease and a similarly rapid process was noted in two patients with connective tissue disease (eosinophilic fasciitis and rheumatoid disease), possibly related to the administration of penicillamine.

The association of chronic eosinophilic pneumonia and rheumatoid disease has not, to my knowledge, been reported in the literature. Three patients with histologically proven bronchiolitis obliterans are presented, two of whom had rheumatoid disease. All three patients had, in addition, clinical and radiological evidence of chronic eosinophilic pneumonia with histological confirmation in two. The data are examined in the light of the hypothesis that the association in these patients of chronic eosinophilic pneumonia and rheumatoid disease with bronchiolitis obliterans is more than coincidental.

Case reports

Case 1 A 34-year-old woman had a six-year history of allergy with positive skin testing for housedust, moulds, and various foodstuffs, recurrent nasal polypi, and peripheral eosinophilia. She was admitted on 5 June 1979 for review of persistent disabling polyarthritis. She had first noted generalised joint pains without objective signs in 1974. In 1978 a clinical diagnosis of bilateral sacroiliitis was made; a latex test at that time was strongly positive on two occasions. From December 1978 she developed aches in the fingers, ankles, and back, and redness and swelling developed in the wrists, proximal interphalangeal joints, elbows, knees, ankles, and feet. Morning stiffness was pronounced. X-ray of the hands showed spindle-shaped prominence of the soft tissues adjacent to the proximal interphalangeal joints of both index fingers and the left middle finger. No bony abnormality was seen. The patient, a non-smoker, also complained at that time of a hacking cough, productive of only small amounts of mucoid sputum. She experienced sweats and chills at night but was apyrexial. There was no history of inhalation of toxic fumes, nor had she been taking tetracycline, nitrofurantoin, or penicillamine.

On admission she was not acutely ill. She had obvious vitiligo of face, neck, arms, forearms, abdomen, and lower back. Blood pressure was 120/80 mm Hg. She was afebrile. Examination of the respiratory system revealed bilateral soft inspiratory rales, more marked on the right. Musculoskeletal examination revealed tenderness and swelling of proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, knees, ankles, and small joints of the feet. Synovial thickening and effusions...
were noted in the knees and ankles. There was limitation in the range of movement of elbows, shoulders, and knees.

Investigations revealed a sedimentation rate of 55 mm in 1 hour. The peripheral eosinophil count was 1428/mm³ on 14 June and this had risen to 3210/mm³ by 20 June. Examination of stools for ova cysts and parasites was negative. Skin testing for candida was negative. Mantoux test (5 TU) was negative. Rheumatoid latex test was positive 1:10240. Antinuclear factor was very weakly positive. Anti-deoxyribonucleic acid (anti-DNA) levels were normal. Viral serology was negative. Serum immunoglobulin estimation was normal apart from a marginal elevation of IgG. Serum complement was normal. A chest x-ray on admission revealed multiple peripheral pulmonary infiltrates, and review at this time of a routine chest x-ray taken in March 1979 disclosed a peripheral zone of increased density in the posterior segment of the left upper lobe. Marked progression in these peripheral infiltrates was noted on a chest x-ray by 19 June. Pulmonary function studies (Table 1) showed a restrictive pattern of disease.

Table 1  *Pulmonary function tests*

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<th>Case 1</th>
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<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>3-08</td>
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<tr>
<td>FRC (l)</td>
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</tr>
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<td>1-50</td>
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<tr>
<td>FVC (l)</td>
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<td>2-20</td>
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<tr>
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A = initial presentation; B = one month later; C = 7-12 months later.

Values in parentheses are percent predicted.

Open lung biopsy was carried out two weeks after admission. This showed diffuse infiltration of lung interstitium and flooding of alveoli by eosinophils (Fig. 1a). Central necrosis of these eosinophils was seen in some alveoli. The alveoli also contained a fibrinous exudate and numerous lipid-filled macrophages. Multinucleate (Touton) giant cells were present within alveoli (Fig. 1b), and these were seen also within the lumina of some bronchioles, where destruction of adjacent bronchiolar wall with proliferation of fibroblastic tissue gave the lesion a granulomatous appearance (Fig. 1c). More striking was the widespread obliteration of bronchiolar

Fig. 1  Case 1. (a) Open lung biopsy. There is flooding of alveoli and infiltration of pulmonary interstitium by numerous eosinophils. To the left of centre a typical eosinophilic abscess is seen. Lipid-laden macrophages intermingle with eosinophils within the alveoli (Haematoxylin and eosin; original magnification × 160). (b) Multinucleate (Touton) giant cells lie in alveolar spaces. Eosinophils permeate all areas of the lung parenchyma (H and E; original magnification × 160). (c) Granulomatous destruction of the wall of a bronchiole by giant cell and fibroblastic infiltrates. This appearance was seen quite frequently in different areas of the biopsy (H and E; original magnification × 63). (d) A polypoid fibroblastic proliferation protrudes into the bronchiole, partly obliterating the lumen. Eosinophils are present within the polyp. This histological variant of bronchiolitis obliterans predominated throughout the specimen (H and E; original magnification × 63). (e) Concentric constriction of the bronchiolar lumen by mucosal fibrous tissue. Constrictive bronchiolitis obliterans, as seen here, was noted infrequently in the biopsy specimen. (Elastic van Gieson; original magnification × 63).
lumina by polypoid masses of fibroblastic tissue mixed with eosinophils (Fig. 1d). Occasional bronchioles showed circumferential constriction of the lumen by mucosal fibrous tissue (Fig. 1e). Follicular bronchiolitis was noted focally in several sections. The interstitium contained, together with many eosinophils, a moderate infiltration of lymphocytes and plasma cells. Vasculitis was not marked, although infiltration of the walls of some vessels by eosinophils was seen. Granulomas were not seen. Several small bronchi were included in the biopsy specimen; these showed prominent goblet cell metaplasia of the epithelium, plugging of the bronchi with mucus in which eosinophils were trapped, thickening of the bronchial basement membrane, and mild hypertrophy of the bronchial muscle. Special stains for organisms were negatives and cultures from the biopsy tissue were negative for fungi, acid-fast bacilli, and bacteria. Immunofluorescence studies for IgG, IgA, IgM, C3, C4, C1q, and fibrin showed only weak positivity for fibrin within alveoli.

Steroid therapy (prednisone 60 mg orally per day) was started on 11 July. Five days later the peripheral eosinophil count was normal. A chest x-ray three days later showed considerable clearing of the infiltrates. Pulmonary function studies the next day, showed some improvement (Table 1). Serial radiographs over the next two months showed almost complete clearing of the infiltrates. The latex test on 10 October was negative. The patient remains well apart from arthritis.

CASE 2
A 58-year-old housewife was admitted from another hospital on 10 May 1971 with a presumptive diagnosis of pulmonary tuberculosis. She had first presented eight weeks previously because of a progressive cough productive of one-quarter of a cup of mucopurulent sputum per day, fever, increasing dyspnoea and fatigue, and a loss of 3-5 kg in weight. There was no history of wheezing or of arthritis. Past history was non-contributory. She had not inhaled toxic fumes. She had not been treated with nitrofurantoin or para-amino salicylic acid, but on initial presentation she had received a short course of tetracycline. The patient was a non-smoker and had no allergies at that time. A nephew was reported to have asthma.

Examination on admission revealed a pyrexia of 38.8°C, a respiratory rate of 24/min, and blood pressure 110/70 mm Hg. There were signs of right lung consolidation, and inspiratory rales were present over both lower lobes. No clinical evidence of airways obstruction was found. A chest x-ray showed bilateral pulmonary infiltrations, more marked on the right, with a suggestion of a peripheral distribution (Fig. 2a). The peripheral blood eosinophil count was 2400/mm³. Rheumatoid factor (latex fixation test) was positive 1:640. Antinuclear factor was negative. Sedimentation rate was 124 mm/h. Skin tests for fungi were negative. Stool examination for ova, cysts, and parasites was negative. Allergy

![Fig. 2 Case 2. (a) Frontal radiograph 11 days after admission. Patchy consolidation of both lungs is seen, more marked on the right. There is some suggestion of a peripheral distribution of the infiltrates. (b) Dramatic clearing of pulmonary infiltrates three weeks after the institution of steroid therapy.](http://jcp.bmj.com/)

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testing was negative at that time. Serological titres for respiratory viruses and mycoplasma were negative. Bacterial, mycobacterial, and fungal cultures on sputa were negative. Pulmonary function studies showed a restrictive pattern (Table 1). The patient was treated with antituberculous drugs (isoniazid, streptomycin, and ethambutol) without improvement.

Open lung biopsy was carried out two weeks after admission. This showed diffuse thickening of alveolar walls with an increase in interstitial collagen (Fig. 3a). Alveoli contained lipid-filled macrophages together with some eosinophils; in some regions, flooding of alveoli by eosinophils was evident, and in these areas central necrosis of eosinophils was seen. Eosinophils and plasma cells widely infiltrated the interstitial tissues, and lymphocytes were numerous also in these areas. Isolated multinucleate (Touton) giant cells were present within alveoli. There was pronounced hyperplasia of alveolar type II cells, and foamy macrophages were seen also beneath the epithelium. No granulomas were evident. A striking feature also in this biopsy specimen was the presence of polypoid masses of granulation tissue, which extended into the lumina of small bronchioles, partly occluding them (Fig. 3b).
Although the vessels showed marked sclerosis, there was no evidence of vasculitis.

Administration of prednisone, 40 mg/day, was begun on 28 May 1971. Within a few days dramatic clinical and radiographic improvement occurred, and this continued over the next few weeks (Fig. 2b). Pulmonary function studies one month later showed a return to normal (Table 1). The steroid treatment was gradually reduced and finally discontinued after six months.

One month later (December 1971), however, the patient noted a return of dyspnoea with wheezing. Clinical examination revealed hyperinflation of the chest, bronchovesicular breath sounds, and scattered expiratory rhonchi. Chest x-rays confirmed the clinical impression of hyperinflation. Lung function studies (Table 1) showed changes typical of obstructive lung disease.

The patient was seen once more in July 1975. She had a cough productive of mucoid sputum and an exacerbation of dyspnoea and wheezing. Peripheral eosinophilia, 1055 eosinophils/mm³, was again present. Skin testing revealed positive reactions to trees, moulds, weeds, feathers, gum, and hog. Clinical and radiographic evaluation showed little change since December 1971. She returned finally in December 1976 because of inflammation, swelling, and tenderness of metacarpophalangeal and proximal interphalangeal joints of the left little and ring fingers. At that time rheumatoid factor (latex test) was negative.

CASE 3

This 69-year-old woman had a history of rheumatoid disease which dated back 33 years. The disease initially affected shoulders, hands, and feet but eventually progressed to involve almost all the joints, including the temporomandibular joints. Medical treatment had included acetyl salicylic acid, gold, and steroids but penicillamine was not given. She had had surgery to both knees and to the feet (excision of metatarsal heads). Biopsies of both knees showed typical rheumatoid synovitis. Before this admission she had not had steroid treatment for two years. In the past she had had intermittent peripheral eosinophilia as high as 2400/mm³ (1974). Latex fixation test was negative in 1959 and 1974 and positive 1:640 in 1972. Antinuclear factor was repeatedly negative; LE cells were repeatedly negative; anti-DNA levels were normal. Radiographic examination of the joints in 1974 showed changes of rheumatoid disease in the cervical spine, knee, and shoulder joints. The metatarsal heads had been removed by that date. A chest x-ray was reported as normal in 1973. Unfortunately, as the patient had died two years before the preparation of this report no x-rays were available for examination.

The patient’s terminal admission extended from April 1977 to February 1978. She presented in April 1977 with extreme breathlessness of four days’ duration. Clinical examination of the respiratory system revealed bilateral crepitations. A chest x-ray on admission showed bilateral patchy upper lobe infiltrates. Peripheral eosinophilia was again documented (up to 13%); a polymorphonuclear leucocytosis was not observed. Mantoux test (5 TU) was negative. Repeated bacteriological studies of blood, sputum, throat, and urine were negative. In the absence of specific proof of infection steroid treatment was begun. Serial radiographic examinations showed clearing of the upper lobe infiltrates over the next five weeks. Pulmonary function studies one month after admission, however, showed evidence of severe airflow obstruction. A chest x-ray in September 1977 showed no evidence of pulmonary infiltrates, but the patient’s clinical course from admission to the time of death in February 1978 was one of slowly progressive respiratory failure.

Examination of the lungs at necropsy revealed bilateral hyperinflation. The bronchi contained mucoid secretions, and an established bronchiolitis obliterans (Fig. 4) was seen in a patchy distribution

![Fig. 4](http://jcp.bmj.com/)

*Fig. 4 Case 3. Established bronchiolitis obliterans seen in a patchy fashion throughout multiple lung sections at necropsy. (H and E; original magnification × 25).*
throughout multiple sections of both lungs. Focal interstitial scarring was also noted.

Table 2 summarises the relevant features of the above cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>CEP</th>
<th>BO</th>
<th>Rheumatoid disease</th>
<th>Rheumatoid factor</th>
<th>Peripheral eosinophilia</th>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>(definite) 1:10240</td>
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<td>+</td>
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<tr>
<td>2</td>
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<td></td>
<td>1:640</td>
<td>+</td>
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<tr>
<td>3</td>
<td>?</td>
<td>+</td>
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CEP = chronic eosinophilic pneumonia; BO = bronchiolitis obliterans; + present; – not present.

Discussion

The association of chronic eosinophilic pneumonia (CEP) and rheumatoid disease with bronchiolitis obliterans as documented above may simply be coincidental. It is possible that the associated diseases merely increased the risk and severity of bronchiolitis obliterans in these patients. The similarities between the cases are such, however, that the hypothesis of a more than coincidental association of CEP, bronchiolitis obliterans, and rheumatoid disease merits exploration.

The clinical courses of cases 1 and 2 conform well to those described in several published reports on CEP.5–11. A history of allergy, night sweats and chills, the abrupt onset of the illness, peripheral blood eosinophilia, peripheral infiltrates on chest x-rays, failure of antibiotic and antituberculous therapy, and the dramatic clinical and radiographic response to steroid therapy are all features typical of CEP as it has been delineated. The absence of fever and dyspnoea in case 1 is usual, but individual cases of CEP without these features have been reported.7 9 10 The radiographic picture in case 2 does not have the classical 'photographic negative of pulmonary oedema' appearance, but Gaensler and Carrington11 have noted that 24% of the cases in their series lacked the typical appearance. Case 2 also was given a short course of tetracycline early in her illness. CEP is known to occur in association with several drugs,6 7 and Ho and his associates12 have implicated tetracycline in this context. Both of their patients, however, had a typical hypersensitivity skin rash and improved on withdrawal of the drug, neither of which features was seen in this case.

The finding that first attracted attention to cases 1 and 2 was the very marked bronchiolitis obliterans that was evident in the lung biopsy of each patient. This was far more severe and widespread than is usually seen in CEP.6 7 10 Supporting the severity of bronchiolitis obliterans in case 2 was the florid obstructive pneumonitis seen in the related parenchyma. After a dramatic response to steroids in this patient, with reversal of the restrictive pattern of disease seen on admission, the later development of a clearly obstructive picture apparently related to small airways disease (MMEFR = 1.20 l/s; Table 1) is striking. In the published series of CEP in which functional studies are provided, four patients are relevant in this context: one patient6 had a picture of combined restrictive and obstructive disease (histological features not specified); one patient8 with histological evidence of CEP and (mild) bronchiolitis obliterans continued to have obstructive disease after resolution of CEP; and two patients7 developed, respectively, moderate and marked obstruction after CEP (neither of these had bronchiolitis obliterans on lung biopsy). In the light of these observations, the subsequent course of case 1 will be of extreme interest regarding the development of an obstructive picture.

Case 1 is of interest in two further ways. By the criteria of the American Rheumatism Association18 she has definite (but not classical) rheumatoid disease. The association of CEP and rheumatoid disease has not previously been suggested. However, some patients with rheumatoid disease develop peripheral eosinophilia, which is both sporadic and unexplained.14 Further, such patients have a higher incidence of extra-articular manifestations of rheumatoid disease (including pulmonary fibrosis).14 Patients with rheumatoid disease are known to be more liable to pulmonary infection.15 It is conceivable that, in such a population (often steroid-treated), fleeting pulmonary infiltrates attributed to infection, together with peripheral eosinophilia, might in fact represent 'silent' CEP. One of 16 patients with CEP reported by Liebow and associates6 was noted incidentally to have a latex fixation test positive 1:320. Examination of the lung biopsy in that case showed a granulomatous reaction in the wall of bronchioles (their Fig. 30) identical with that seen in Fig. 1c in this paper. This appearance was not seen in any other patient in the group. One patient with CEP in the series of Gaensler and associates11 later developed arthritis and scleroderma (serology is not reported).

The second point of interest in case 1 is the relevance of histological bronchiolitis obliterans to the rheumatoid disease. Geddes and associates8 documented five patients with rheumatoid disease who developed rapidly progressive bronchiolitis obliterans. In their cases the bronchiolitis obliterans was of the less common constrictive variety described by Gosink and colleagues,16 one of whose patients also had rheumatoid disease. A similar histological pattern was seen in the rheumatoid
patient with bronchiolitis obliterans described by Epler and associates.\textsuperscript{4} Disease in this patient was attributed possibly to penicillamine (although two of Geddes' patients were not treated with this drug). A further case of bronchiolitis obliterans in a patient exposed to cleansing agents\textsuperscript{37} was more likely related to that patient's rheumatoid disease.\textsuperscript{18} Bronchiolitis obliterans in cases 1 and 2 was predominantly of the more common polypoid type, but occasional bronchioles in the biopsy specimen from case 1 (Fig. 1e) showed circumferential constriction by mucosal fibrous tissue identical with that seen in Fig. 12 of the paper by Geddes and associates.\textsuperscript{3} The appearance in the same patient of both polypoid and constrictive bronchiolitis obliterans is distinctly unusual\textsuperscript{16} and raises once more the question of the relevance of this patient's rheumatoid disease.

It is clear that case 2 does not have rheumatoid disease. However, the positive latex fixation test noted during her CEP and the transient episode of small joint inflammation in December 1976 may yet prove to be of significance. Pulmonary complications of rheumatoid disease are known occasionally to precede the arthritis by months or years.\textsuperscript{19,20} This patient had histological bronchiolitis obliterans in 1971 and now has clinical evidence of this disease.

Case 3 incorporates many of the speculative issues raised thus far. This patient with classical rheumatoid disease was noted at necropsy, after a progressive terminal illness of 10 months' duration, to have established bronchiolitis obliterans. There is circumstantial evidence to suggest that the illness that initiated her terminal admission was an episode of CEP: acute onset of dyspnoea, failure to demonstrate an infective aetiology, peripheral eosinophilia, bilateral upper lobe radiographic infiltrates, and a radiographic response to steroid therapy. This may in effect have been a clinically 'silent' CEP, as suggested above, with subsequent progression to the bronchiolitis obliterans seen at necropsy.

The aetiology and pathogenesis of CEP and of many cases of bronchiolitis obliterans are unknown. Certainly the common infectious agents have been ruled out in many cases. In support of an immunological basis for pathogenesis in CEP, Kanner and Hammar\textsuperscript{21} have identified within the dilated rough endoplasmic reticulum of large plasma cells a homogeneous intracisternal electron-dense material which they presume to be immunoglobulin. They suggest that this may act as an eosinophilic chemoattractive factor. In this regard, the cases reported here are contributory only in that once again an infectious cause seems unlikely, and an immune one seems at least possible.

Accepting an association between bronchiolitis obliterans and rheumatoid disease,\textsuperscript{3} the cases presented here raise three questions. Firstly, is there an association between CEP and rheumatoid disease? Second, can CEP progress to bronchiolitis obliterans? And, finally, in rheumatoid disease, is bronchiolitis obliterans on occasion a late manifestation of CEP? The evidence provided here is by no means conclusive, but it is hoped that the description of these cases may stimulate further observations in this field. Parallel studies of CEP, bronchiolitis obliterans, and rheumatoid disease will be required to provide the answers.

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