Bronchiolitis obliterans organising pneumonia in patients taking acebutolol or amiodarone

PHILIPPE CAMUS, JEAN-NOËL LOMBARD, MARIELLE PERRICHON, FRANÇOISE PIARD, JEAN-CLAUDE GUÉRIN, FRANÇOISE BÉJUI THIVOLET, LOUIS JEANNIN

From the Service de Pneumologie et de Réanimation Respiratoire, Centre Hospitalier Universitaire, and Laboratoire d'Anatomie Pathologique, Faculté de Médecine, Dijon, and the Service de Pneumologie and Service d'Anatomie Pathologique, Hôpital de la Croix Rousse, Lyon, France

ABSTRACT Two patients, treated with acebutolol and amiodarone respectively, developed a disease clinically, radiologically, and pathologically indistinguishable from bronchiolitis obliterans organising pneumonia. In one case recovery followed discontinuation of acebutolol; in the other case cessation of amiodarone had no effect, and corticosteroids were required. In addition to these patients, several cases of bronchiolitis obliterans organising pneumonia have been reported during treatment with gold salts, amiodarone, and miscellaneous other drugs. Taken together, this information supports the view that bronchiolitis obliterans organising pneumonia may be a form of response by the lungs to insult by drugs.

Introduction

As a result of recent reports,1-3 there has been renewed interest in the clinicopathological entity called bronchiolitis obliterans with organising pneumonia. Patients with this condition usually present with mild constitutional symptoms that have lasted for several weeks.1-3 The chest radiograph usually shows bilateral asymmetrical, sometimes migrating, alveolar opacities.1-3,5 Pathologically, bronchiolitis obliterans organising pneumonia is characterised by buds of connective tissue obliterating alveoli, alveolar ducts, and bronchioles, associated with active interstitial inflammation.1-4 On these grounds the disease differs from both pure bronchiolitis obliterans and classic interstitial pneumonia. Its cause or causes have not been clearly identified. The disease has been observed in the context of gastrointestinal disorders,6 certain lung infections,7 connective tissue disease,8 and inhalation of toxic fumes.9 In most cases, however, the exact cause remains obscure. We report two patients who developed bronchiolitis obliterans organising pneumonia while being treated with acebutolol and amiodarone respectively.

Case reports

CASE 1

A 59 year old man, who was employed in road construction, was admitted to hospital in January 1987. He gave a one month history of non-productive cough, increasing dyspnoea, a 4 kg weight loss, and moderate fever (< 38°C). He was a former smoker (30 pack years). For the past two years he had received acebutolol (Sectral, Specia, Paris) 200 mg/day for systemic hypertension (cumulative dose 219 g). On examination dry crackles were heard, mostly over the right lung. The chest radiographs (fig 1) showed numerous alveolar opacities, predominantly on the right side. The white cell count was normal; the erythrocyte sedimentation rate was 74 mm in one hour; serum electrophoresis displayed a normal pattern; and no precipitins against common avian, thermoactinomycete, or Aspergillus antigens were detected. Immunological investigations showed no circulating immune complexes and normal levels of complement C3, C4, and CH50. Antinuclear antibodies and rheumatoid factor were absent. Pulmonary function tests showed a restrictive pattern (total lung capacity (TLC; helium dilution) 62% predicted, vital capacity (VC) 63% pred, FEV1/forced vital capacity (FVC) 70%). Carbon monoxide transfer was near normal (81% pred). Arterial hypoaemia and hypopacnia were found (arterial oxygen tension (Pao2) in room air 7.3 kPa; carbon dioxide tension (Paco2)
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4.6 kPa. Bronchoalveolar lavage fluid had normal cellularity (total cell count $160 \times 10^6/\text{l}$) and an increased proportion of neutrophils (15% of all lavage fluid cells). A transbronchial lung biopsy specimen from the right middle lobe showed the combination of organising pneumonia and obstruction of small air passages by buds of connective tissue (fig 2). After discontinuation of acebutolol the fever remitted rapidly. Lung volumes and the chest radiograph improved more slowly over two months, at the end of which the fluid from a second lavage showed a normal neutrophil count and a shift in the cells towards eosinophils (12%) and lymphocytes (24%). By the

Fig 1  Patient 1: Chest radiograph at the time of admission showing bilateral, predominantly right sided alveolar shadows.

Fig 2  Patient 1: Transbronchial lung biopsy specimen showing the combination of increased cellularity, organising pneumonia, and alveolar and ductal fibrosis (left). (Haematoxylin-eosin-safranin.)

eighth month lung volumes were normal (VC 1001% pred), but slight airflow obstruction persisted (FEV$_1$/FVC 69%). When last evaluated in March 1989 the patient was symptom free and had a normal chest radiograph.

CASE 2
An 81 year old retired turner was admitted to hospital

Fig 3  Patient 2: Chest radiographs showing (left) retraction alveolar shadows in the right upper lobe at admission and (right) clearing of the right upper lobe, lesions of the right middle and lower lobes, and a moderate pleural effusion one month after withdrawal of amiodarone.
in October 1987 because of moderate weight loss and fever, persistent dyspnoea, and a cough productive of yellowish sputum. The symptoms had developed over several weeks and had not changed after a 10 day course of amoxycillin. A chest radiograph in July 1987 had been normal. He was a former cigarette smoker. In 1984 a permanent pacemaker had been implanted for the control of cardiac arrhythmia, and he started to take amiodarone (Cordarone, Clin-Midy-Labaz, Montpellier) 200 mg/day, five days a week (cumulative dose 190 g). He was also receiving isosorbide dinitrate, aminophylline, canrenone (an antialdosterone diuretic), and frusemide. On examination dry crackles were heard over the right upper lung field. A mild leucocytosis was noted (12 × 10⁹/l); the erythrocyte sedimentation rate was 20 mm in the first hour. The biochemical profile was normal. The chest radiograph showed retraction and shadowing of the right upper lobe (fig 3, left). Pulmonary function tests showed substantial airflow obstruction (FEV₁/FVC 42%); TLC was 74% and VC 55% of predicted. Mild hypoxaemia (Pao₂ 7-9 kPa) and slight hypocapnia (Paco₂ 4-8 kPa) were present. Bronchoalveolar lavage fluid had increased cellularity (1-5 × 10⁹/l) and a substantially increased neutrophil count (80%). A similar pattern was found in lavage fluid from the right middle lobe, though this area was not affected on the chest radiograph. Amiodarone was discontinued but the remainder of the treatment was kept unchanged, and the patient was discharged. One month later he reported similar symptoms. On the chest radiograph the right upper lobe had spontaneously cleared, and alveolar opacities had migrated toward the right lower lung field (fig 3, right). A moderate pleural effusion was also noted, which proved to be an exudate. Fluid from a second lavage again showed neutrophil alveolitis, but this was less severe (15%). Lung biopsy specimens obtained by thoracoscopy showed severe interstitial pneumonitis and extensive obliteration of alveolar ducts and alveoli by typical “bourgeois conjonctifs” (fig 4). Occasional foci of foamy alveolar cells were also present. Prednisolone 40 mg/day was started in December 1987, with considerable symptomatic improvement and the chest radiograph cleared progressively; pulmonary function test results remained unchanged. Prednisolone was progressively tapered and stopped in August 1988, with no recurrence of the disease.

Discussion

Both patients presented with a history of malaise, dyspnoea, moderate fever, asymmetrical alveolar opacities, and increased neutrophils or lymphocytes in bronchoalveolar lavage fluid. Extensive obstruction of air passages and alveoli by buds of connective tissue, and increased interstitial cellularity were present in both specimens (figs 2 and 4). The outcome was good in both cases. These findings are not specific, but taken together strongly suggest bronchiolitis obliterans organising pneumonia.¹-⁴

As bronchiolitis obliterans organising pneumonia is a non-specific and patchy pattern of lung reaction that may be found in the vicinity of more specific processes,¹ a large biopsy sample is clearly preferable to establish the diagnosis. In a given patient, however, if the clinical features and radiographs pattern strongly suggest bronchiolitis obliterans organising pneumonia and the pathological material obtained by transbronchial biopsy, even if small, is unequivocally character-

Fig 4  Patient 2: Thoracoscopic lung biopsy specimen. Upper panel: lower power view showing widespread atelectasis and extensive obliteration of airspaces by buds of connective tissue with a branched pattern typical of airway dichotomy. Part of the atelectasis may result from a crushing artefact. Lower panel: Higher magnification view showing substantial interstitial infiltration by mononuclear cells, organising pneumonia, and buds of connective tissue. (Haematoxylin–eosin-safranin.)
Corticosteroids are not always effective, we believe that the risks of an open lung biopsy are not justified. In such instances a therapeutic trial of corticosteroids should be considered.

Bronchiolitis obliterans organising pneumonia has been observed in the context of exposure to toxic fumes, Nocardia asteroides infection, gastrointestinal disorders, and connective tissue disease. Our patients fitted none of these categories, and apart from their exposure to drugs their disease was entirely similar to idiopathic bronchiolitis obliterans organising pneumonia.

Patient 1 developed bronchiolitis obliterans organising pneumonia while receiving acebutolol, a drug previously associated with lung infiltrates. As withdrawal of the drug without addition of corticosteroids led to prompt and lasting recovery, we believe that acebutolol was implicated in this patient's illness. The histological changes in drug induced lung disease due to acebutolol have been described briefly as consisting of granulomas; the presence of bronchiolitis obliterans organising pneumonia was not reported.

Patient 2 was receiving several drugs in addition to amiodarone, but none of them has been previously associated with pulmonary side effects. In contrast to patient 1, withdrawal of the possible offending drug had no effect on his disease. This does not rule out amiodarone induced lung disease, as this drug is known to sequester in the lung for a long time. Several reports on amiodarone pneumonitis have mentioned bronchiolitis or alveolar fibrosis, or both, in addition to the classic pattern of interstitial pneumonitis with foamy alveolar macrophages. In addition, we are aware of two unpublished observations of typical bronchiolitis obliterans organising pneumonia in patients taking amiodarone (F Galateau, personal communication, 1989). Usually, however, bronchiolar or alveolar fibrosis is less prominent than in our patient. On the other hand, cases of amiodarone pneumonitis have been reported in which lung opacities recurred months after withdrawal of the drug, at a time when corticosteroids were being gradually tapered. Although this observation is consistent with the known persistence of amiodarone in the lung, it is very reminiscent of bronchiolitis obliterans organising pneumonia.

Our cases should also be viewed in the light of earlier reports of bronchiolitis obliterans organising pneumonia in patients treated with other drugs. It was observed in single patients treated with barbiturates and D-penicillamine. Williams et al independently reported the condition in patients with ulcerative colitis treated with sulphasalazine and mesalazine respectively. In the latter paper bronchiolitis obliterans organising pneumonia was ascribed to ulcerative colitis on the basis of an earlier report of this association. Typical histological features have also been observed in open lung biopsy specimens of three patients with rheumatoid arthritis and gold induced pneumonitis. Given that all these drugs are known to induce classic drug induced interstitial pneumonitis, we may speculate that in certain patients bronchiolitis obliterans organising pneumonia represents a pattern of response by the lungs to insult from drugs.

In summary, our observations, coupled with several published reports, suggest that bronchiolitis obliterans organising pneumonia may develop in patients treated with various drugs. To establish whether a connection exists between exposure to a drug and bronchiolitis obliterans organising pneumonia, we believe that a careful history of drug intake should be recorded in every patient with this condition.

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