Obliterative bronchiolitis with atypical features: CT scan and necropsy findings

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ABSTRACT: We describe the natural history of cryptogenic bronchiolitis obliterans in a patient followed for 24 yrs with serial pulmonary function tests and radiology. Severe, progressive airway obstruction developed, with overinflation but preservation of Kco. There was progressive hypoxaemia, which worsened on exertion; hypercapnoea was modest until late in the illness. Neither bronchodilators nor steroids were effective. The chest radiograph remained normal; CT showed irregular areas of low attenuation peripherally throughout the lungs, with Hounsfield numbers typical of emphysema, but no bullae. Postmortem studies included histology and quantitative studies of a corrosion cast of one lung. They showed marked airway narrowing at all levels, with pruning of peripheral branches, mucus plugging, and some emphysema. The case illustrates that cryptogenic bronchiolitis obliterans may be chronic and difficult to distinguish clinically or by investigation from other forms of chronic obstructive airways disease, particularly emphysema.


Progressive airway obliteration (bronchiolitis obliterans or obliterative bronchiolitis) appears to be a distinct pathological entity, sometimes in association with connective tissue disorders, or following inhalation of fumes or viral infections [1–3]. Cases have also been reported following heart-lung and bone marrow transplantation [4, 5], but a substantial proportion of cases are of unknown aetiology [6]. The condition is rare, and causes diagnostic difficulty by simulating other airway obstructive syndromes. Confusion also arises from the nomenclature, since the term bronchiolitis obliterans has been applied not only to an entity affecting just the airways [2, 6], but also to a condition which combines airway obliteration and organizing pneumonia (bronchiolitis obliterans organizing pneumonia [7] or cryptogenic organizing pneumonia [8]).

We describe the clinical course and investigations in a case of obliterative bronchiolitis, in which we had the opportunity to do very extensive functional investigations in life and postmortem studies.

Case history

The patient was a female, aged 43 yrs at the time of first presentation, with a 4 yr history of dyspnoea, cough, and wheezing. She was, and remained, a nonsmoker, and had not been exposed to toxic fumes. During the ensuing 24 yrs until her death, the patient remained under hospital care. In this time, many diagnostic labels were applied, including "asthma", "chronic bronchitis", "emphysema", and "chest infection". On one occasion only, 13 yrs after presentation, tubercle bacilli were isolated from her sputum, and she was treated with rifampicin and isonicotinic acid hydrazide (INAH) for 15 months. However, her chest radiograph at that time, and throughout her life, remained normal, and there was no convincing sputum microbiological evidence of airway infection during episodes when the patient complained of cough. History and serology were negative for rheumatoid arthritis. Several bronchoscopies over the years revealed normal appearance, and bronchial biopsies showed nonspecific inflammatory changes only. From presentation until death from ventilatory failure 24 yrs later, the patient had 19 admissions with ventilatory failure.

Pulmonary function

Spirometric tests were performed at intervals throughout the course of the illness. Typical values obtained when the patient was stable are given in table 1; they show severe, progressive airways obstruction. Initially, there was some response to inhaled bronchodilators, but this was not sustained, and there was never a convincing response to trials of oral or inhaled steroids.
Thoracic computerized tomographic (CT) scan

Thoracic (CT) scan showed increased radiolucency in the periphery of both lungs, particularly in the mid and lower zones. The structure of the central parts of both lungs looked normal. Hounsfield numbers, measured according to the protocol of ROSENBLOOM et al. [9] gave a mean value of 927, which is outside the normal range (747–863), and within the range for emphysema in this hospital (837–931).

Exercise tests

Exercise tests were performed on a treadmill with monitoring of oxygen saturation and end-tidal CO₂. The capnogram showed no end-tidal plateau, and was used only to give a direction of change. On air, the saturation fell to 78% after very mild exercise. Subsequent exercise runs were, therefore, carried out on oxygen administered by nasal catheter. Unlike the situation at rest, oxygen administration during exercise did not result in worsening hypercapnia. It was eventually possible to obtain a total walking distance of 670 m in 12 min, with oxygen delivered at 4 l/min.

Clinical course of ventilatory failure

The pattern of ventilatory failure was not typical of chronic obstructive pulmonary disease (COPD). In a good phase, one year prior to death, arterial carbon dioxide tension (Paco₂) was 49 mmHg (6.5 kPa), with an arterial oxygen tension (Pao₂) breathing air of 68 mmHg (9.1 kPa) and a pH of 7.38. The Paco₂ never went above 64 mmHg (8.5 kPa) until the final illness, and blood gases during sleep were not worse than during the daytime. Without oxygen, the Paco₂ during exacerbations dropped to between 40–50 mmHg (5.3–6.7 kPa). Throughout the course of the illness, alveolar to arterial oxygen difference (A–AD0₂) was elevated even during remissions (20–44 mmHg (2.7–5.9 kPa)), and towards the end of the illness the patient was considered for domiciliary oxygen. However, increased inspired oxygen at rest was accompanied by hypercapnia; for example, administration of 2 l/min of oxygen by nasal cannulae, which elevated resting Paco₂ from 50 to 80 mmHg (6.7 to 10.7 kPa), caused a rise of Paco₂ from 51 to 82 mmHg (6.8 to 10.9 kPa) over 6 h, accompanied by headache, drowsiness, and flapping tremor. Oxygen therapy was, therefore, not instituted. Some episodes of ventilatory failure, but not all, seemed to be precipitated by infection (as judged by purulent sputum), and some episodes were accompanied by oedema, in which diuretics appeared to confer benefit [10]. Bronchodilators and steroids did not help symptomatically, and were not accompanied by convincing improvements in the peak flow chart. During the final admission, which was prompted by another episode of ventilatory failure, the patient suffered a respiratory arrest from which she could not be resuscitated.

### Table 1. Serial tests of spirometry before and after inhaled bronchodilators

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>FEV₁</th>
<th>FVC</th>
<th>Pre-BD</th>
<th>Post-BD</th>
<th>Pre-BD</th>
<th>Post-BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>1.06</td>
<td>2.40</td>
<td>1.29</td>
<td>2.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>0.65</td>
<td>2.05</td>
<td>0.76</td>
<td>2.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>0.65</td>
<td>1.94</td>
<td>0.85</td>
<td>2.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>0.40</td>
<td>1.20</td>
<td>0.55</td>
<td>1.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>0.40</td>
<td>1.10</td>
<td>0.40</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predicted range of forced expiratory volume in one second (FEV₁) 1.3–2.8 l. Predicted range of forced vital capacity (FVC) 2.1–3.7 l. BD: bronchodilator.

### Table 2. Detailed pulmonary function tests during last year of life

<table>
<thead>
<tr>
<th>Test</th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRC l</td>
<td>3.60</td>
<td>1.77–3.61</td>
</tr>
<tr>
<td>TLC l</td>
<td>4.87</td>
<td>3.78–5.90</td>
</tr>
<tr>
<td>RV l</td>
<td>2.98</td>
<td>1.16–2.64</td>
</tr>
<tr>
<td>RV/TLC %</td>
<td>61</td>
<td>28–50</td>
</tr>
<tr>
<td>Dco mmol·min⁻¹·kPa⁻¹</td>
<td>3.76</td>
<td>4.70–5.90</td>
</tr>
<tr>
<td>Kco mmol·min⁻¹·kPa⁻¹·l⁻¹</td>
<td>1.35</td>
<td>1.21–2.01</td>
</tr>
</tbody>
</table>


During a major review 1 yr prior to death, lung volumes and gas transfer measurements were also obtained (table 2). They demonstrate over-inflation, similar to the changes described in obliterative bronchiolitis by TUCKO et al. [6]. In addition, the expiratory flow-volume curve showed a grossly scalloped shape, indicative of expiratory airway collapse, and the total lung capacity (TLC) measured by single breath helium dilution was almost 2 l less than the steady-state value, implying severe mal-distribution of inspired gas. These latter features are very typical of small airway obstruction. The carbon monoxide transfer coefficient (Kco) was within the normal range.

### Ventilation-perfusion lung scan

Ventilation-perfusion lung scan was performed with krypton-81m as the inspired gas. There was gross irregularity of ventilation and perfusion in both lungs, with more marked abnormality in the lower zones, where ventilation and perfusion had almost ceased. The ventilation and perfusion defects were matched, and the appearances were nonspecific and consistent with either obstructive airways disease or any diffuse destructive process.
**Postmortem findings**

The postmortem findings were unremarkable, except for the lungs and thickening of the wall of the right ventricle. The lungs were congested, the larger bronchi containing mucus and shed bronchial epithelium. Some medium and small bronchi contained material not typical of mucous plugging. The left lung was used to make a bronchial cast and the right was used for histological studies. Inflation with fixative was much slower than normal.

**Histological findings**

Most of the bronchi and large bronchioles were partly, and in some areas completely, filled with acid and neutral mucins, with occasional neutrophils. Alveolar capillaries were congested, with some extravasation of red cells into alveoli, which also contained increased numbers of macrophages and shed pneumocytes. There were occasional small irregular fibroelastic scars in the periphery of the lung, in which the bronchioles were completely absent, but the accompanying pulmonary arteries were present and normal. In one scar, there was a small airway completely surrounded and compressed by fibrous tissue. In places, there was a subpleural, bandlike zone of fibroelastic scarring, with entrapped small airways, and deep to this there were large dilated airways, some of which were filled with mucus. There was extensive and severe emphysema, mainly centriacinar, but in places panacinar, which was more marked in those subpleural areas which did not show scarring. There were small foci of pneumonic consolidation.

**Lung cast**

The left lung was separated by division of the left main bronchus, and was used to make a bronchial cast. Firstly, the airways were repeatedly washed out with a solution of acetylcysteine, in order to remove as much mucus as possible. Then, the bronchus was cannulated and a resin cast was made of the airways, using the method described by Horsfield et al. [11]. The lungs were macerated in a solution of sodium hydroxide, 120 g·l⁻¹, and the cast was washed clean with water and dried. A drawing was made of the branching pattern of the cast, generations were counted on the drawing, and the diameters of the branches were measured and recorded. Diameters were measured at the midpoint of the length of each branch, using a dial caliper calibrated to 0.05 mm and read to the nearest 0.025 mm. Where the cross-section appeared to be noncircular, two readings were made at right angles and the mean value used.

The cast showed obvious marked loss of peripheral branches, whilst those branches which had cast were thin and spindly (figs 1a and b). By choice, we would have preferred to measure the cast using Strahler orders [11], but owing to loss of branches this proved to be impossible. Instead, the branches were classified by

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**Fig. 1.** Resin casts of the airways obtained from: a) normal lungs and b) patient's lungs.
generation, with the main bronchus as generation 0, and counting downwards one generation at each bifurcation. A plot was then made of diameter on a logarithmic scale against generation.

Unlike Strahler orders, which normally give a straight line plot with these variables, generations give a plot which fans out from the point for the main bronchus (figs 2a and b). In order to demonstrate any change in the

Diameters of the branches, this plot was compared with that obtained from a cast made at autopsy from the lungs of a 25 year old man dying of diabetic complications with no history of lung disease and normal postmortem lung appearances [12]. Figures 2a and b show the results obtained from the upper and lower lobes, respectively, of the normal and the patient's lung. It may be seen that apart from the first two branches of the lower lobe bronchus, the range of diameters for each generation in the patient's cast is markedly below that for the normal cast. This indicates that there is a generalized narrowing of the lumina of the airways, whilst the cast as a whole demonstrates the loss of many small bronchi and bronchioles.

Discussion

Bronchiolitis obliterans is a pathological entity, involving obstruction of bronchioles by organizing exudate, polypoid masses of granulation tissue, or mural and extramural fibrosis [1, 2]. It may follow damage to the lower respiratory tract by infection or inhaled toxic fumes, may accompany connective tissue disorders or host-graft reactions, or may arise spontaneously. The clinical course is variable; it is often progressive, but may run a very chronic course [6], as in our case. The condition presents considerable diagnostic difficulty, particularly when there is no known precipitant. As our investigations show, the syndrome can be indistinguishable from smoking-related obstructive airways disease on criteria of lung function, radiology (including CT scan), blood gases, and isotope lung scans. The diagnostic difficulty was only resolved postmortem by the typical histological features of end-stage bronchiolitis obliterans, supplemented by information from the cast.

Confusion about the condition and its natural history has arisen, not only from the rarity of bronchiolitis obliterans, but also from the use of the same term to describe a different entity ("bronchiolitis obliterans organizing pneumonia" [7], or "cryptogenic organizing pneumonia" [8]) in which the major feature is alveolar pathology. As two recent editorials [13, 14] have emphasized, these conditions in general present separable clinical syndromes, even though there is some overlap in the list of possible precipitants. Patients with bronchiolitis obliterans organizing pneumonia have relatively minor airway pathology, and show radiological and CT evidence of patchy infiltrates, and a restrictive, rather than an obstructive, functional disturbance, as well as often responding to steroids [15]. Our patient, who demonstrated progressively severe fixed airway obstruction (tables 1 and 2), a normal chest radiograph, but CT evidence of severe overinflation, and deteriorating ventilatory failure, was typical of the group with pure obliterative bronchiolitis.

We did not perform a bronchogram, but the lung cast made at postmortem is not dissimilar to the bronchograms published by TURTON et al. [6] and GIDDIES et al. [2] in bronchiolitis obliterans, with marked pruning of peripheral airways. This finding must be interpreted with
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References