

Bronchiolitis obliterans following the ingestion of an Asian shrub leaf

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Introductory article

Outbreak of bronchiolitis obliterans associated with consumption of *Sauropus androgynus* in Taiwan

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Background. In August, 1995, there was an outbreak in Taiwan of rapidly progressive respiratory distress associated with consumption of uncooked *Sauropus androgynus*, a vegetable with a claimed yet unconfirmed effect on weight control. We report on 23 patients with strikingly similar clinical presentations. **Methods.** A structured questionnaire for clinical manifestations was completed. Radiographic findings, pulmonary physiological changes, immunological and microbiological studies, and pathological examination were evaluated. **Findings.** All patients were young and middle-aged women (mean age 39 years [range 21–52]). They took uncooked *S androgynus* juice, generally mixed with guava or pineapple juice, for a mean duration of 10 weeks. Progressive dyspnoea and persistent cough were the main symptoms on presentation. Pulmonary function testing uniformly revealed moderate to severe airflow obstruction with mean forced expiratory volume in 1 s (FEV₁) of 0.66 L (26% of predicted). No bronchodilator response was observed. Room-air arterial blood gas analysis showed hypoxaemia (mean PaO₂ 9.6 [SD 1.6] kPa). Chest radiographs were essentially normal. High-resolution computed tomography showed bilateral bronchiectasis and patchy low attenuation of lung parenchyma with mosaic perfusion. Ventilation-perfusion scintigraphic findings were compatible with obstructive lung disease. Histopathology of open lung biopsy specimens in four patients confirmed the presence of bronchiolitis obliterans. Immunohistochemical stains of the open lung biopsy specimens showed predominance of T cells over B cells. Immunofluorescent stains for IgG, IgM, IgA, C1q, C3, and C4 were negative. Serum concentrations of tumour necrosis factor α were higher than those of normal controls. Clinical response to prednisolone was limited. **Interpretation.** We describe an unusual association between bronchiolitis obliterans and ingestion of the vegetable *S androgynus*. T-cell mediated immunity may be involved in the pathogenesis. (Lancet 1996;348:83–5)

The introductory article¹ identifies a potentially important, previously unrecognised, and most unusual cause of obliterative bronchiolitis – a vegetable product ingested in the hope of controlling weight. It reports a clinical study of high quality which not only alerts us to the respiratory hazards of one particular product of the natural environment, but prompts a timely review of two critical aspects of evolving clinical practice in respiratory medicine. These comprise the early diagnostic use of high resolution computed tomographic (HRCT) scanning using inspiratory and expiratory images and the immediate use of specific immuno-suppressant therapy.

The study more obviously reminds the practising clinician that the lungs can be readily damaged by toxic agents whose portal of entry is the gastrointestinal tract not the airways, and that serendipity is often necessary before such a problem is recognised. While pulmonary toxicity from a variety of medications is well recognised

and regulatory mechanisms now greatly limit the chance of important adverse effects in epidemiological terms, the ingestion of unlicensed medications or “fad” foods carries unknown risks and adverse effects are not readily identified. This theme is also discussed in the article on pages S63–7 by Voelkel reviewing pulmonary hypertension in subjects ingesting appetite suppressants.

Uncooked leaf extract of *Sauropus androgynus* (an Asian shrub of the Euphoriaceae family) is, like appetite suppressant drugs, used to control weight though its effectiveness is not proven. Adverse effects are not seen primarily in the pulmonary vasculature, but the introductory article provides very suggestive evidence that it may cause an obliterative bronchiolitis.

Obliterative bronchiolitis

Obliterative bronchiolitis (OB) has remained an enigma, explained in part by common delays in diagnosis.

Furthermore, open lung biopsy – on which until recently the diagnosis has depended – has often been restricted to the most severely affected patients.

The disease is characterised by persistent inflammation of the bronchioli and proliferative occlusion of the lumen with fibroblasts and smooth muscle cells.^{2,3} In many forms the airway disease extends centrally to involve bronchi, which causes bronchiectasis.⁴ However, the alveoli remain free of the disease process unless there is evidence of organising pneumonia. The latter indicates the separate condition of bronchiolitis obliterans and organising pneumonia (BOOP) which has a distinct pathogenesis.⁵

Although OB is not commonly recognised in adults, it is frequently diagnosed in childhood following adenovirus infection and there is a suspicion that it may be caused by respiratory syncytial virus in both children and adults.⁶ Other established causes include autoimmune diseases such as rheumatoid arthritis, and the inhalation of a number of toxic chemicals such as ammonia, chlorine, organophosphates, and nitrogen dioxide.⁷ There is also an association with smoking, but the full significance of this is not yet clear. The disorder has gained particular prominence over recent years because of its occurrence complicating heart and lung transplantation, and this has led to greater urgency in obtaining diagnostic biopsy tissue and in administering prompt immunosuppressive therapy. As a result, there have been important advances in understanding the pathogenesis of OB and in modifying its natural history. The novel discovery that it may also occur commonly in populations ingesting the natural products of certain plants will usefully emphasise its importance in the spectrum of environmentally induced disorders of the airways.

Obliterative bronchiolitis attributable to *Sauropus androgynus*

During a remarkable period of less than six months more than 60 patients who had ingested juice containing uncooked leaf extract of *Sauropus androgynus* presented to the Veterans General Hospital-Kaohsiung in Taiwan with progressive undue breathlessness. In the study population of 23 patients the breathlessness was severe and they were admitted, but the size of the population ingesting the extract from which the initial 60 were drawn (the denominator) is not known. The epidemiological significance of the outbreak described by Lai and colleagues¹ is consequently unclear, particularly as news media interest stimulated many of the initial presentations.

The 23 patients reported by Lai *et al*¹ were all women and non-smokers, and all had been well previously. Five had bought the leaf extract as a juice from local stores and 18 had used home made preparations. The authors remarked that the extract was commonly uncooked when consumed, though is more generally used in Taiwan after cooking. Cooking might therefore “de-toxify” the relevant inducer of the bronchiolar disease. Significant heat denaturation would, however, reduce the possibility that the pulmonary reaction was a consequence of papaverine within the fresh leaves (about 580 mg/100 g) since this is resistant to such levels of heat. The leaf extract was apparently consumed in considerable quantities (estimated range 2–21 kg over 10 weeks, mean 8 kg), so other components will merit consideration as the primary inducing agent.

All 23 patients had progressive undue breathlessness and 21 had cough which was usually non-productive.

There was generally tachypnoea with impaired breath sounds, and there were crackles in 17 and wheezes in three. The mean forced expiratory volume in one second (FEV₁) was only 26% of predicted and forced vital capacity (FVC) 51%, and there was no significant response to a bronchodilator. A raised mean residual volume but not total lung capacity indicated air trapping, but the corrected gas transfer factor for carbon monoxide (TLCO) was said to be normal in 17. The diagnosis rested essentially on the appearances on the HRCT scan which showed patchy low attenuation of the lung parenchyma with a mosaic perfusion pattern in the expiratory images of all patients and in the inspiratory images of 11. All scans additionally showed bronchiectasis in the segmental and subsegmental bronchi. The plain radiographs were essentially normal.

Four patients underwent open lung biopsy which revealed the characteristic appearance of OB with a predominance of T lymphocytes. There was no histological or serological evidence of infection, and material from two biopsy specimens gave negative results when cultured for viruses. The authors speculated that the disease was immunologically mediated.

Neither bronchodilator nor corticosteroid medication had any discernible effect, and there was no spontaneous resolution once ingestion of the leaf extract was discontinued. Severe respiratory impairment was, however, already established before the diagnosis was confirmed in any subject. The authors did not report whether there was continued progression after ingestion ceased.

Obliterative bronchiolitis after heart-lung and lung transplantation

The introduction of lung transplant surgery has provided an opportunity to study the natural history of an immunologically “driven” form of OB. In the heart-lung transplant population followed by the Stanford group the first descriptions of the presentation, physiology, pathology, and natural history of the disease were described.³ Breathlessness and coughing from progressive airflow obstruction were the principal findings associated with the characteristic pathology.

Numerous descriptions followed but a detailed analysis of lung transplant recipients⁸ appeared to indicate that the main risk factor for OB was the frequency of acute rejection in the first three months after surgery. This complication is now the major long term cause of death after lung transplantation and accounts for a significant amount of morbidity. New forms of immunosuppression including inhaled corticosteroids may delay the development of the disease.

The lessons learnt from transplantation include the value of identifying a progressive fall in FEV₁ as a characteristic of OB, which cannot be improved even with intense immunosuppressive treatment. Another is the nature of the inflammatory process and of the T lymphocytes which appear to orchestrate the fibroproliferative occlusion of the small airways and cause the bronchiectasis.⁹ This observation lends support for the principle of early diagnosis and the use of enhanced immunosuppressive treatment in the hope of limiting the rate of decline in FEV₁.

An obliterative bronchiolitis is also seen after bone marrow transplantation, again driven by an immune process, where graft cells injure the host’s airways in a “graft versus host” disease.¹⁰ Augmented immunosuppressive treatment does offer a means of limiting the rate of progress of this form of disease.

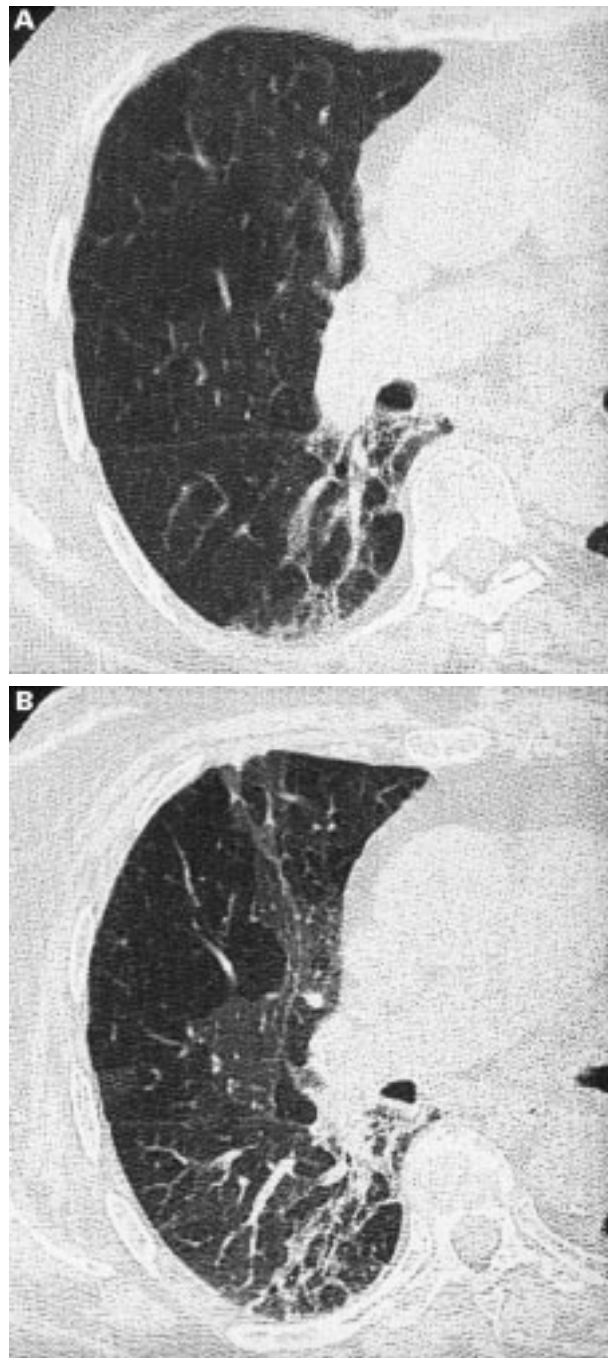
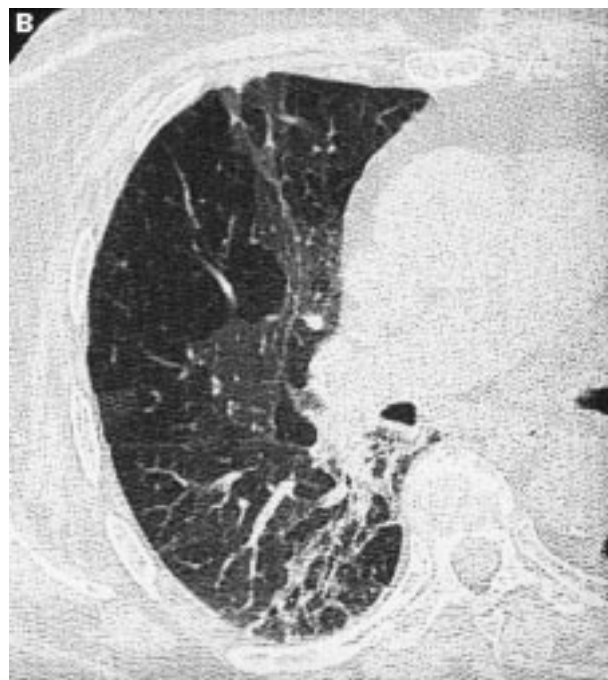


Figure 1 High resolution CT scan in inspiration and expiration. The inspiratory image (A) shows a few fibrotic strands posteriorly but the remaining lung parenchyma is unremarkable. Expiration is inevitably associated with lung movement so two expiratory images are shown. In both B (matched for lung level) and C (matched for spinal level) the images show marked variability in attenuation of the lung parenchyma. The more translucent areas identify localised air trapping and bronchiolar disease. (Courtesy Dr W Simpson).



Diagnostic tests for OB

In patients who undergo lung transplantation the observation of a progressive fall in FEV_1 without evidence of reversibility provides the first indication of the disease. The $TLCO$ is usually maintained, as is seen in other forms of OB.¹¹ The chest radiograph is also normal in appearance, which usefully separates OB from BOOP where irregular, often bilateral, alveolar shadowing is seen.

Progressive irreversible airflow obstruction in transplant patients has proved to be almost always a consequence of OB, so further investigation is not generally indicated. Open lung biopsy, in particular, is no longer required. For sporadic cases in the population at large, however, there are many potential alternative causes of irreversible airflow obstruction and a progressive decline in FEV_1 . These include emphysema, asthma, obstructive chronic bronchitis, bronchiectasis, eosinophilic granuloma, and sarcoidosis. Physiological tests can help

to identify emphysema where the low FEV_1 is associated with reduced $TLCO$ and increased total lung capacity, but for most patients alternative measures are usually required.

The diagnosis has depended traditionally on an open lung biopsy, and until the recent introduction of video-assisted thoracoscopy biopsy procedures were reserved for those patients with advanced disease and marked disability – that is, those who have “earned” this ultimate diagnostic test.^{2,12} Video-assisted thoracoscopy has greatly reduced the risks of lung biopsy where tissue samples beyond the size available from endobronchial procedures are required, and biopsy via thoracoscopy is indicated when there is a rapid decline in FEV_1 despite high dose corticosteroid treatment. Values of FEV_1 below one litre often indicate a poor prognosis irrespective of the nature of the underlying disease, and biopsy specimens are commonly taken in these circumstances in non-smoking patients without evidence

LEARNING POINTS

- * Obliterative bronchiolitis (OB) may be induced by the ingestion of an agent present in (or contaminating) the leaf of *Sauropus androgynus*, an Asian shrub.
- * The inducing agent is yet to be identified, but may be susceptible to heat denaturation in cooking.
- * OB is best recognised from characteristic CT appearances of patchy low attenuation and a mosaic pattern of perfusion in expiratory images.
- * Rapid diagnosis coupled with the identification and elimination of the inducing cause is essential to the prevention of serious respiratory disablement.
- * The early use of immunosuppressive therapy may ameliorate the tendency towards progressive disease.

of emphysema. The characteristic pathology is selective involvement of the small airways and proliferative obliteration of the lumina with fibromuscular cells. Inflammatory cells, usually lymphocytes, are seen in the earlier stages. Once there is advanced fibrotic obliteration, little can be offered to the patient in terms of treatment, so there has been a quest for methods of earlier diagnosis.

The introduction of HRCT scanning of the thorax has brought a welcome revolution in clinical practice. The use of high speed scanners and imaging of the lung in both full expiration and inspiration has enabled gas trapping and hence bronchiolar disease to be identified reliably.^{13 14} Those regions of the lung subserved by narrowed small airways fail to deflate on expiration and retain a low attenuation compared with normal regions. This produces a variegated appearance of low and high attenuation areas. The “patchwork” or “mosaic” appearance on expiration is characteristic of OB and is shown in fig 1. The HRCT scan also allows any bronchiectasis to be demonstrated and the exclusion of interstitial diseases, emphysema, and sarcoidosis.^{15 16} Its use early in the investigation of patients with irreversible airflow obstruction may offer increased hope of successful therapeutic intervention.

Pathogenesis of OB

Little is known of the common pathway towards the obliterative airway process of the different forms of OB. Injury to airway epithelium appears to be a common element. This may be the first step from which lymphocyte infiltration is initiated. As described in the introductory article, T cell lymphocytes are involved, not only in the immunologically driven forms as in lung transplantation, but also when ingestion or inhalation of a probable exogenous toxin is involved. Experimental OB has shown that selective suppression of the T cell infiltrate with an agent such as rapamycin “blocks” the subsequent fibromuscular proliferation which is the hallmark of the later stages of the disease.

Treatment of OB

In lung transplant patients, who are at high risk of developing OB after experiencing three or more rejection episodes in the first three months of transplantation, it has proved possible to prevent OB. This has been achieved by the use of nebulised high dose budesonide, a corticosteroid which locally reduces lymphocyte in-

filtration whilst avoiding the consequences of high dose oral steroids. Trials are currently underway to study the effect of inhaled steroids in OB from other causes such as graft versus host disease and rheumatoid disease. The same approach might be of value early after toxin ingestion or inhalation injury.

For the patient with advanced disease, where the principal pathology is of progressive fibrous obliteration of the airways, transplantation of the lungs is the main therapeutic option. In these patients, when there is no evidence of bronchiectasis, a single lung transplant is effective. A double lung transplant is required if there is concomitant bronchiectasis. There is no evidence that OB occurs more frequently after transplantation in patients who have OB as an original diagnosis. Selection of patients for transplantation requires evidence of a poor prognosis, and generally requires an FEV₁ below one litre (or less than 30% predicted),¹⁷ or dependency on supplemental oxygen.

Conclusions

The description of an outbreak of OB associated with an “environmental” toxin serves to alert us to the possibility of causes of small airways disease unassociated with cigarette smoking or asthma. The introduction of high speed HRCT scanning to detect gas trapping from small airways disease offers an opportunity for early diagnosis of this devastating disease. From our experience of lung transplantation it now seems possible that, with “early” intervention with specific immunosuppressants such as rapamycin or inhaled high dose corticosteroids, it might be possible to “blunt” the progressive loss of functioning small airways. It is important from the clinical, pathological and therapeutic viewpoints to separate OB from BOOP.¹⁸

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