Bronchiolitis obliterans following the ingestion of an Asian shrub leaf

T W Higenbottam
Department of Respiratory Medicine, Royal Hallamshire Hospital, Sheffield, UK

Introductory article

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

R-S Lai, AA Chiang, M-T Wu, J-S Wang, N-S Lai, J-Y Lu, L-P Ger, V Roggli

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. Immuno-fluorescent 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.

The introductory article 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 immunosuppressant 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 563–7 by Voelkel reviewing pulmonary hypertension in subjects ingesting appetite suppressants.

Uncooked leaf extract of Sauropus androgynus (an Asian shrub of the Euphorbiaceae 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 (OB) has remained an enigma, explained in part by common delays in diagnosis.
Taiwan after cooking. Cooking might therefore "de-lymphocytes which appear to orchestrate the fibro-
remarked that the extract was commonly uncooked with intense immunosuppressive treatment. Another is ingesting the extract from which the initial 60 were that the main risk factor for OB was the frequency of heat. The leaf extract was apparently consumed in An obliterative bronchiolitis is also seen after bone graft cells injure the host's airways in a progressive air-flow obstruction were the principal findings associated with the characteristic pathology. 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 fibro-proliferative occlusion of the small airways and cause bronchiectasis. 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. Augmented immunosuppressive treatment does not mean of limiting the rate of progression of this form of disease.

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 re-
sponse 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 (T lc) 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 of OB with a predominance of T lymphocytes. There was no histo-

logical 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 bronchial nor corticosteroid medication had any discernible effect, and there was no spontaneous resolution once ingestion of the leaf extract was dis-
continued. 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.
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 bronchioalveolar disease. (Courtesy Dr W Simpson).

Diagnostic tests for OB

In patients who undergo lung transplantation the observation of a progressive fall in FEV₁ without evidence of reversibility provides the first indication of the disease. The Tlco is usually maintained, as is seen in other forms of OB. 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 FEV₁. These include emphysema, asthma, obstructive chronic bronchitis, bronchiectasis, eosinophilic granuloma, and sarcoidosis. Physiological tests can help to identify emphysema where the low FEV₁ 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. 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 FEV₁ despite high dose corticosteroid treatment. Values of FEV₁ 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...
LERNING 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 inspiratory 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.

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 injury.literation, 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 evidence of bronchiectasis, a single 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 35% predicted).13 14 Dependency on supplemental oxygen

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 doses of budesonide, a corticosteroid which locally reduces lymphocyte infiltration whilst avoiding the consequences of high doses of 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 35% predicted).13 14 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.15


13 Meurer NL, Mahr RR. Diseases of bronchioles. CT and histopathological findings. Radiology 1993; 188: 3-12.


Bronchiolitis obliterans following the ingestion of an Asian shrub leaf

TW Higenbottam

Thorax 1997 52: 68
doi: 10.1136/thx.52.2008.S68

Updated information and services can be found at:
http://thorax.bmj.com/content/52/suppl_3/68.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/