

latent EBV genome in the graft BALT results in the post-transplant lymphoproliferative disease evolving rapidly. The chronic antigenic stimulation which occurs with repeated malarial infections is considered to be an important adjunct to EBV in the development of Burkitt's lymphoma.⁸

Bronchial changes have been documented in the presence of pathogenic organisms such as *Aspergillus*.⁹ In case 1 the presence of *Pseudomonas aeruginosa* and *Aspergillus* resulted in therapeutic trials which delayed the diagnosis of post-transplant lymphoproliferative disease.

In the clinical/pathological spectrum of post-transplant lymphoproliferative disease a benign lymphoid proliferative response to EBV may respond to a reduction in immunotherapy and antiviral agents. Early intervention in post-transplant lymphoproliferative disease may therefore prevent the progression of the disease since ganciclovir has been shown to inhibit the development of B cell lymphoma in an immunocompromised mouse model.¹⁰

Ulcerative bronchitis in a heart-lung transplant recipient may be the first sign of post-transplant lymphoproliferative disease, and suggests that BALT in the grafted lung is an important site for the initiation of clonal B cell proliferation in post-transplant lymphoproliferative disease.

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- 1 Nagington J, Gray J. Cyclosporin A immunosuppression, Epstein-Barr antibody and lymphoma. *Lancet* 1980;ii:536-7.
- 2 Thomas JA, Crawford DH. B-cell lymphoma in organ transplant recipients. *Semin Thorac Cardiovasc Surg* 1990;2: 221-32.
- 3 Nalesnik MA, Jaffe R, Starzl T, Demetris AJ, Porter K, Burnham JA, et al. The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisolone immunosuppression. *Am J Pathol* 1988;133:173-92.
- 4 Arrand JR, Rymo L. Characterisation of the major Epstein-Barr virus-specific RNA in Burkitt's lymphoma-derived cells. *J Virol* 1982;41:376-89.
- 5 Armitage JM, Kormos RL, Stuart S, Fricker FJ, Griffith BP, Nalenik M, et al. Posttransplant lymphoproliferative disease in thoracic organ transplant patients: ten years of cyclosporine-based immunosuppression. *J Heart Lung Transplant* 1991;10:877-87.
- 6 Yousem SA, Randhawa P, Locker J, Paradis IL, Dauber JA, Griffith BP, et al. Posttransplant lymphoproliferative disorders in the heart-lung transplant recipients: primary presentation in the allograft. *Hum Pathol* 1989;20:361-9.
- 7 Richmond I, Pritchard GE, Ashcroft T, Corris PA, Walters EH. Bronchus associated lymphoid tissue (BALT) in human lung: its distribution in smokers and non-smokers. *Thorax* 1993;48:1130-4.
- 8 Editorial. Epstein-Barr virus and AIDS-associated lymphomas. *Lancet* 1991;338:979-81.
- 9 Kramer MR, Denning DW, Marshall SE, Ross DJ, Berry G, Lewiston NJ, et al. Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. *Am Rev Respir Dis* 1991;144:553-6.
- 10 Boyle TJ, Tamurini M, Berend KR, Kizilbash AM, Borowitz MJ, Lyerly HK. Human B-cell lymphoma in severe combined immunodeficient mice after active infection with Epstein-Barr virus. *Surgery* 1992;112:378-86.

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Obliterative bronchiolitis caused by multiple tumourlets and microcarcinoids successfully treated by single lung transplantation

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Abstract
Histological examination of a lung removed at transplantation revealed multiple peripheral tumourlets and microcarcinoids in close association with bronchioles causing an obliterative bronchiolitis. This was an unexpected

finding but explained the progressive airflow limitation which characterised the patient's clinical course.

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Multiple tumourlets arising in the lung are usually regarded as benign although they can show malignant potential.¹ They share a similar phenotype to carcinoid tumours, both showing neuroendocrine features but no cytological evidence of malignancy.² Unlike true carcinoids they are rarely of clinical significance, although a recent report suggests that they may be associated with airways obstruction.³ We describe a patient in whom multiple pulmonary tumourlets and microcarcinoids occurred within the small airways resulting in a progressive obliterative bronchiolitis and severe airflow limitation. This was successfully treated by single lung transplantation.

Case report

A 42 year old white woman presented with a 10 year history of progressive airflow limitation. She had previously smoked a total of five pack-years. Pulmonary function tests showed: forced expiratory volume in one second (FEV₁) (% predicted) 840 ml (28%), forced vital capacity (FVC) 3160 ml (89%), peak expiratory flow

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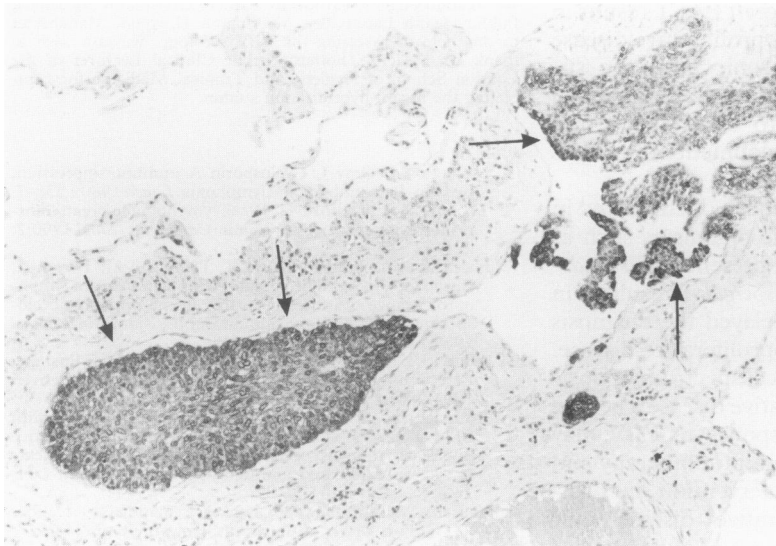


Figure 1 Section of lung showing proliferation of neuroendocrine cells within a bronchiole causing obliteration of the lumen (arrows). Cells are immunostained with an antibody to chromogranin A. Magnification $\times 300$ reduced to 60% in origination.

rate (PEFR) 155 l/min (37%), residual volume (RV) 2950 ml (143%), total lung capacity (TLC) 6200 ml (105%), carbon monoxide transfer factor (TLCO) 6.64 mmol/min/kPa (73%), carbon monoxide transfer coefficient (Kco) 1.82 mmol/min/kPa/l (108%). The chest radiograph showed hyperinflated lungs with several 5 mm opacities in the right lung. Fiberoptic bronchoscopy was normal and a ventilation/perfusion scan showed multiple small matched defects. Her disease did not respond to bronchodilator or oral corticosteroid therapy. She was considered to have an obliterative bronchiolitis with "benign" pulmonary opacities, possibly related to old pulmonary tuberculosis, and over the next 11 years her condition remained stable.

At the age of 53 she returned with a six month history of severe breathlessness on exertion. She had no history of viral pneumonia or rheumatoid disease. Her only medication was metoprolol for hypertension. On physical examination her chest was hyperexpanded and there were bilateral basilar inspiratory crackles. The haemoglobin concentration was 15.3 g/dl, white cell count $6.5 \times 10^9/l$ with a normal differential count, and erythrocyte sedimentation rate was 4 mm/hour. The serum α_1 -antitrypsin level was 2.1 g/l (normal range 0.8–3.0 g/l) and an autoantibody screen was negative. The chest radiograph showed hyperinflated lungs and multiple 5 mm opacities. Computed tomographic scanning showed minimal bronchial wall thickening and dilatation, and attenuation of the pulmonary vessels suggestive of obliterative bronchiolitis together with multiple nodules in both lungs. There was no evidence of emphysema. Repeat lung function tests showed severe airflow limitation: FEV₁ 480 ml (15%), FVC 1990 ml (56%), PEFR 141 l/min (33%), RV 3670 ml (177%), TLC 5820 ml (98%), TLCO 4.63 mmol/min/kPa (50%), and Kco 1.55 mmol/min/kPa/l (91%). There was no improvement following a further trial of oral corticosteroids.

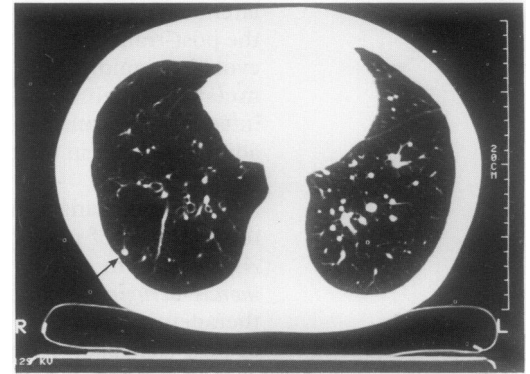


Figure 2 Computed tomographic scan of the lower lobes. The transplanted left lung appears normal. The segmental and subsegmental bronchi in the native right lung are dilated and slightly thickened. The pulmonary vasculature is attenuated and there is a 4 mm peripheral nodule (arrow).

In view of this decline the patient was assessed for single lung transplantation and underwent successful surgery in June 1991. The resected lung contained multiple peripheral parenchymal nodules varying from 2 mm to 10 mm in diameter. Microscopically these consisted of central areas of fibrosis surrounded by islands of uniform cells extending into surrounding lung. The cells were positive on immunostaining for neurone specific enolase, chromogranin A, bombesin, and calcitonin, confirming their neuroendocrine origin (fig 1). Many of the nodules were adjacent to pulmonary arterioles and appeared to have obliterated the accompanying bronchioles by inducing fibroblast proliferation and connective tissue deposition. There was no evidence of lymph node metastases.

The patient remains well two years after transplantation. Repeat computed tomographic scanning of the thorax confirms that the pulmonary nodules persist in the right lung but there is no evidence that these have progressed during immunosuppressive therapy (fig 2). There is also no evidence that nodules have developed in the transplanted lung, nor is there evidence of rejection.

Discussion

Carcinoid tumours account for 1–6% of primary lung tumours and usually occur as solitary lesions in proximal bronchi.⁴ Those occurring peripherally may be multiple but are usually an asymptomatic radiological finding.⁵ The term "carcinoid tumourlet" was first used by Whitwell to describe microscopic collections of neuroendocrine cells bordering bronchiolar airspaces in the peripheral lung.⁶ They generally measure less than 4 mm in diameter, are multiple, and occur only in the lung periphery, while carcinoid tumours are more likely to be central, solitary, and measure more than 1 cm.^{1,2,7} However, lesions between 4 mm and 10 mm in diameter have been described and confusion about their nomenclature remains.⁷ Confusingly, multiple lesions of less than 2 mm with cervical lymph node metastases have also been labelled carcinoid tumours.⁸ We prefer to call lesions between 4 mm and 10 mm

"microcarcinoids" as originally described by Gould *et al.*⁷

Tumourlets are rare, being found in only 17 of 7800 necropsies² and in 22 of 2300 lungs resected surgically.⁶ They are usually multiple and discovered as an incidental finding on light microscopy. Although more common in patients with chronic lung disease such as bronchiectasis,⁹ they can occur in normal lung.² Morphologically they resemble carcinoid tumours and rarely the two conditions occur together.

There have been few reported cases in which tumourlets have given rise to symptoms. Skinner and coworkers reported a 20 year old man who presented with diarrhoea, miliary shadowing on chest radiography, and a mild restrictive defect on lung function tests. Open lung biopsy revealed multiple carcinoid tumourlets.⁸ Millar and coworkers described a 53 year old woman who presented with cough, haemoptysis, multiple pulmonary nodules up to 12 mm in diameter, and a mild mixed restrictive and obstructive ventilatory defect. Open lung biopsy revealed nodules of proliferating neuroendocrine cells surrounded by fibrous tissue in relation to and distorting bronchioles.¹⁰ In both these patients the disease ran an apparently benign course with metastatic spread occurring only to local lymph nodes.

Recently a series of six patients with idiopathic diffuse hyperplasia of neuroendocrine cells and airways obstruction has been reported by Aguayo *et al.*³ All presented with breathlessness but none had any physical signs. Pulmonary nodules were apparent on chest radiography in four. In two others the chest radiograph was normal but a computed tomographic scan showed diffuse bronchial wall thickening and areas of hyperlucency suggestive of gas trapping. In one the computed tomographic scan also showed multiple (<10 mm) pulmonary nodules. All these patients had evidence of airflow limitation on lung function tests but there was no consistent pattern to the lung volumes or carbon monoxide transfer factor, which presumably vary with the relative degrees of fibrosis and gas trapping. In four of these patients the condition had remained stable after a mean follow up of seven years. The remaining two developed progressive airflow limitation and attempts to treat this with chemotherapy were unsuccessful.

These authors suggested that the obliterative

bronchiolitis was caused by the proliferating endocrine cells and we would propose a similar mechanism in the present case. Two lines of evidence support this theory. Firstly, on microscopic scrutiny of the lung we did not observe obliterative bronchiolitis in the absence of neuroendocrine proliferations. Secondly, it is known that neuropeptides such as bombesin, secreted by neuroendocrine cells, have the potential to activate human lung fibroblasts *in vitro*.

As far as we are aware, our patient is the first to be successfully treated by single lung transplantation which is, at present, the only viable therapy when this condition is progressive. In the past this operation was only performed on patients with fibrotic lung disease. However, it has now been successful in selected patients with obstructive lung disease and pulmonary vascular disease.

It may be possible to make the diagnosis in such patients by immunostaining of a trans-bronchial biopsy sample. This was not performed in our patient because of the risk of pneumothorax. Similarly, open lung biopsy is invasive and may not be advisable in patients with severe airflow limitation. The computed tomographic appearances we describe are similar to one of the patients reported by Aguayo *et al.*³ The constellation of computed tomographic signs of obliterative bronchiolitis, together with multiple pulmonary nodules, should suggest the diagnosis of tumourlets and microcarcinoids.

- 1 D'Agate D, Persin H. Carcinoid tumourlets of the lung with metastasis to a peribronchial lymph node. *Cancer* 1985; 55:2472-6.
- 2 Churg A, Warnock ML. Pulmonary tumourlet: a form of peripheral carcinoid. *Cancer* 1976;37:1469-77.
- 3 Aguayo SM, Miller YE, Waldron JA, Bogin RM, Sunday ME, Staton GW, *et al.* Idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease. *N Engl J Med* 1992;327:1285-8.
- 4 Hurt R, Bates M. Carcinoid tumours of the bronchus: a 33 year experience. *Thorax* 1984;39:617-23.
- 5 Bonikos DS, Bensch KG, Jamplis RW. Peripheral pulmonary carcinoid tumours. *Cancer* 1976;37:1977-88.
- 6 Whitwell F. Tumourlets of the lung. *J Pathol Bacteriol* 1955; 70:529-41.
- 7 Gould VE, Linnoila I, Memoli VA, Warren WH. Neuroendocrine components of the bronchopulmonary tract: hyperplasias, dysplasias and neoplasm. *Lab Invest* 1983; 49: 519-37.
- 8 Skinner C, Ewen SWB. Carcinoid lung: diffuse pulmonary infiltration by a multifocal bronchial carcinoid. *Thorax* 1976;31:212-9.
- 9 Cureton RJR, Hill IM. Malignant change in bronchiectasis. *Thorax* 1978;33:131-6.
- 10 Millar MA, Mark GJ, Kanarek D. Multiple peripheral pulmonary carcinoids and tumourlets of carcinoid type with restrictive and obstructive lung disease. *Am J Med* 1978; 65:373-8.