Epstein-Barr virus associated graft failure following heart/lung transplantation


Abstract
A case is described of late pulmonary graft failure in a heart/lung transplant recipient. The major characteristics were alveolar fibrosis and a restrictive physiological deficit. Epstein-Barr virus was implicated as an aetiological agent using immunohistochemical analysis and by a response to treatment with ganciclovir.

Keywords: Epstein-Barr virus, pulmonary fibrosis, obliterative bronchiolitis, lung transplant, bronchiolitis obliterans organising pneumonia.

The major limiting factor to the long term success of lung transplantation is the development of obliterative bronchiolitis within the graft which presents as a predominantly obstructive physiological pattern associated with fibrosis and obliteration of the terminal bronchioles of the graft.1 In contrast, we describe a female patient who developed graft failure with a pure restrictive physiological deficit associated with dominant interstitial fibrosis and the presence of Epstein-Barr virus (EBV) within the lung tissue.

Case report
A 31 year old woman received a heart/lung transplant for Eisenmenger syndrome. She suffered a complete vagotomy at the time of the operation and required a pyloroplasty four weeks following transplantation. A barium study showed slow but satisfactory gastric emptying and no evidence of aspiration. She was maintained on cisapride (Prepulsid) 10 mg at night. Three months following discharge she developed a pyrexia associated with nasal congestion. A routine transbronchial biopsy specimen demonstrated A3a (mild) rejection associated with a marked eosinophilic infiltrate without systemic eosinophilia. She received augmented oral steroids 1 mg/kg for 14 days. A follow up transbronchial biopsy specimen revealed resolution of perivascular cuffing but a persistence of the eosinophilic infiltrate. In the absence of demonstrable infection she then received 500 mg methylprednisolone intravenously on three consecutive days. Because of a progressive decline in lung volumes and a persistent pyrexia she was maintained on high dose oral prednisolone (1 mg/kg reduced by 5 mg per week), in addition to cyclosporin and azathioprine. An autoantibody screen was negative. A thoracic computed tomographic (CT) scan 16 weeks after transplantation demonstrated an acinar infiltrate suggestive of infection. Four consecutive bronchoalveolar lavages (BAL) and transbronchial biopsies failed to reveal an infective agent or evidence of aspiration but demonstrated progressive pulmonary fibrosis. In the presence of ongoing pyrexia and a restrictive physiological defect suggestive of bronchiolitis obliterans organising pneumonia (BOOP), she underwent a repeat CT scan followed by an open lung biopsy of the left lung (10 months after transplantation). The CT scan demonstrated widespread alveolar opacification (fig 1). Histologically, the open lung biopsy specimen showed severe interstitial and alveolar fibrosis (fig 2) as well as a few obliterated bronchioles associated with intimal fibrosis, occlusion of arteries and especially veins.

Lymphoproliferative disease was considered a possibility and the open lung biopsy specimen was examined by immunohistochemistry for antibodies used were specific for EBV latent membrane protein and EBV nuclear antigen 2 (EBNA 2) (CS1-4 and PE2, respectively; Dakopatts) using methods previously described.2 These EBV specific markers were absent but further immunohistochemical analysis was performed using monoclonal antibody directed against the EBV membrane antigen gp340/220 (72A1; a gift from S D Hayward) which is a marker of productive EBV replication.3 This reagent identified numerous foci of EBV production (fig 3) further characterised as being within epithelial cells and not infiltrating B cells using appropriate markers (epithelial membrane antigen and CD20; Dakopatts). There was no serological evidence of EBV reactivation (EBNA2/IG capsid serology) or cytomegalovirus infection (CMV antigenemia negative, BAL DEAFF test negative, and lung tissue immunohistochemistry negative) and light microscopy also failed to demonstrate evidence of herpes simplex virus infection. The patient then received a trial of

Figure 1 Thoracic CT scan with contrast demonstrating widespread diffuse alveolar shadowing of both lower lobes.
The acinar changes seen on the first CT scan indicated possible infection and this is a common cause of eosinophilic infiltration in a lung graft. Repeated investigations for potential infective organisms were undertaken and EBV replication within the graft tissue was the only organism identified. The recurrent pyrexia, documented for 28 weeks, was only eradicated ultimately with intravenous ganciclovir. This suggests that active EBV infection was responsible for the pyrexia and possibly the eosinophilic infiltration at the time of presentation. An additional finding which implies that EBV was pathogenic in this case was that, when the explanted lung tissue was re-examined after the pyrexia had lysed and following ganciclovir therapy, there was no evidence of EBV replication.

Obliterative bronchiolitis is considered to represent a manifestation of chronic graft rejection. It is typified histologically by scarring of membranous and respiratory bronchioles with obliteration of the bronchiolar lumen and fibro-intimal thickening of the arteries and veins within the graft. In our case the dominant feature was that of interstitial fibrosis (fig 2). Physiologically, obliterative bronchiolitis is characterised by progressive small airways obstruction. The physiological pattern in our patient was that of a pure restrictive defect. The typical radiological changes seen with obliterative bronchiolitis are those of hyperinflation and associated bronchiectasis. The CT scans of our patient initially demonstrated acinar changes suggestive of infection which progressed in severity to confluent alveolar opacification located predominantly in the lower lobes (fig 1) without evidence of bronchiectasis.

The restrictive flow volume loop in combination with the CT scan appearances were suggestive of BOOP. However the open lung biopsy specimen did not establish this diagnosis. Detailed histological examination demonstrated severe interstitial and, in areas, confluent fibrosis. The histological features of BOOP, including aggregates of connective tissue within bronchioles and alveolar spaces, were absent.

The clinical picture could have been consistent with lymphoproliferative disease. It was for this reason that the blocks taken from the open lung biopsy specimen were examined for the presence of latent EBV. These were negative but revealed evidence of EBV gp340/220-specific staining located within the epithelial cells of the graft. This antigen is diagnostic of EBV replication where virus particles are produced and is not an antigen expressed during viral latency. The absence of serological evidence of EBV reactivation does not exclude active viral replication, as serological change is known to be a poor marker for EBV infection in an immunocompromised host.

Augmented immunosuppression often leads to opportunistic infection. The finding of EBV within the lung tissue of this patient may therefore be viewed as representing passenger virus rather than a pathogen. Examples of this type of controversy are seen with cytomegalovirus...
Pregnancy following a single lung transplant

Diane Parry, Andrew Hextall, V P Robinson, N R Banner, M H Yacoub

Abstract

Successful pregnancy in a single lung transplant recipient has not been reported previously. The long term effect of pregnancy on graft function and management of deteriorating pulmonary function is not defined. This case describes the management, outcome, and problems encountered when a single lung transplant recipient developed a progressive deterioration in pulmonary function during pregnancy, attributed to accelerated obliterative bronchiolitis.

Keywords: lung transplantation, pregnancy, obliterative bronchiolitis.

There have been a number of reports of pregnancy with successful outcome following solid organ transplantation. Most of the information available pertains to renal and heart transplant recipients. With improving survival and functional status after transplantation, more women are able to consider the possibility of starting a family. Single lung transplantation was first performed successfully in 1983. The indications are usually restrictive or obstructive pulmonary disease. This report describes the successful outcome of a pregnancy in a woman following single lung transplantation.

Case report

The patient was a 31 year old white non-smoker who first presented in 1988 at the age of 24 with breathlessness and a dry cough. She had suffered from Raynaud's phenomenon since childhood and had two grand mal fits during adolescence, the last being 10 years previously. A cerebral computed tomographic scan had been normal. A diagnosis of fibrosing alveolitis was made on open lung biopsy and treatment consisted of high dose prednisolone and cyclophosphamide. She continued to receive sodium valproate for her epilepsy.

Her respiratory condition gradually deteriorated and she developed cyclophosphamide related cytisits. She was accepted for a single lung transplant and placed on the waiting list in June 1992. At that stage she was receiving prednisolone 15 mg daily and her forced expiratory volume in one second (FEV1) was 1.06 l (36% predicted), forced vital capacity (FVC) 1.17 l.

In April 1993 she underwent left single lung transplantation. The donor was a 28 year old female non-smoker with no history of cardiopulmonary disease. Total ischaemic time for the procedure was five hours. In the early postoperative period the patient required one course of methyprednisolone (1 g for three days) for acute rejection, and antibiotics for Staphylococcus aureus cultured from sputum. She made a complete recovery.

In April 1994 her exercise tolerance was excellent. She led a full active life and planned marriage. At her annual assessment FEV1 was
Epstein-Barr virus associated graft failure following heart/lung transplantation.

J J Egan, J P Stewart, P S Hasleton, N Yonan, P Bishop, J R Arrand, A N Rahman, K B Carroll and A A Woodcock

Thorax 1996 51: 1160-1165
doi: 10.1136/thx.51.11.1160