Primary pulmonary hypertension: pathologist as patient

ABSTRACT — We describe the case of Julia Polak, an internationally known pathologist with an interest in primary pulmonary hypertension, a condition which she was subsequently diagnosed to have. This was successfully treated by heart/lung transplantation and she was then in the unique position to study and present her own pulmonary pathology. Professor Polak’s case illustrates the difficulty in diagnosis, the frequent failure of medical treatment and an excellent outcome from heart/lung transplantation. Based on a presentation to a clinico-pathological conference at Hammersmith Hospital.

Primary pulmonary hypertension (PPH) is a rare disease with indolent onset of protean symptoms and often unimpressive physical signs on examination. Julia Polak, a 54 year-old pathologist with an international reputation, developed end-stage PPH in 1995. Her case illustrates the advanced stage that the condition can reach before it is realised that something is seriously wrong. Diagnosis is frequently delayed until right heart failure develops, as it may only be at this point that the patient first sees a cardiologist and echocardiography is carried out. After successful treatment by heart/lung transplantation, Professor Polak was able to study the pathology of her own tissues in detail. Her case emphasises the difficulty in recognising the disorder if a cardiovascular cause is not suspected, the failure of medical management and, happily, highlights the excellent result that can be achieved through heart/lung transplantation.

Case history

Professor Polak had taken the appetite suppressant drug, fenfluramine, for more than three months in 1973. She first developed mild dyspnoea on exertion in 1976, asthma being diagnosed in 1984 and treated with β₂-agonists and steroid inhalers. In 1986 she became short of breath on climbing stairs. In 1991 the asthma appeared to have worsened and she had several courses of oral prednisolone. The haematocrit climbed between 1986 and 1995, reaching a maximum of 17.5 g/dl. This was attributed to pseudo-polycythaemia. In March 1995, after venesection with saline replacement, she had a dizzy turn, felt exhausted and could barely walk. In April 1995, Professor Polak was noted to be hypertensive; she was then referred to a specialist in hypertension at another hospital, who found her blood pressure to be 200/100 mm Hg, with tachycardia and a blowing systolic murmur. Catecholamine levels were normal. Echocardiography to measure left ventricular mass showed that the left ventricular cavity was small with an end-diastolic dimension of 33 mm, but the right ventricle was not dilated. An intra-arterial blood pressure study was arranged, but was not carried out because of worsening dyspnoea. When her legs began to swell and her weight increased, Professor Polak was seen by a cardiologist for the first time. Sinus tachycardia with a blood pressure of 170/80 mm Hg was noted and her jugular venous pressure was raised up to her ear lobes. There was an early diastolic murmur (Grade II) and she also had a tender liver. The electrocardiogram (ECG) revealed changes of right ventricular hypertrophy and echocardiography showed a dilated, poorly contracting right ventricle with a tricuspid regurgitant velocity giving a right ventricular pressure of between 80–120 mm Hg. There was pulmonary regurgitation but no structural abnormalities in the heart. The diagnosis of pulmonary hypertension with right ventricular failure was therefore made.

Professor Polak was treated with bed rest, continuous oxygen and anticoagulation with heparin, followed by warfarin. Her chest radiograph showed enlargement of the heart with prominence of the main pulmonary artery and clear lung fields. A ventilation perfusion scan of her lungs showed homogeneous normal ventilation and perfusion with no evidence of pulmonary embolism. Arterial blood gases showed a PaO₂ of 8.1 kPa and PaCO₂ of 4.1 kPa at rest. Cardiac catheterisation confirmed severe pulmonary hypertension with a pulmonary artery pressure of 133/44 mm Hg, and systemic hypertension with an aortic pressure of 195/120 mm Hg. The cardiac index was 1.6 l/min/m². The coronary arteries appeared normal. Treatment was started with amiodipine 5 mg/d, while warfarin and aspirin were continued. A sleep study showed no dips in systemic arterial saturation at night. There was no cardiovascular response to inhaled nitric oxide. A trial of nebulised prosta-cycline (PGI₂) resulted in a rise in systemic arterial saturation from 85% to 95%, a small rise in cardiac output and a fall in calculated pulmonary vascular resistance with no fall in systemic arterial pressure. This small beneficial effect was not augmented by enoximone. A trial of intravenous prosta-cycline in incremental doses brought about a rise in cardiac output and a fall in calculated pulmonary vascular resistance, but the systemic arterial saturation deteriorated to a nadir of 78%.

Increased doses of amiodipine combined with diltiazem...
were gradually introduced in order to try to force maximal relaxation of smooth muscle in the pulmonary arteries. However, her dyspnoea became worse, arterial oxygen saturation fell and there was x-ray evidence of pulmonary congestion. It was evident that there was going to be no significant positive response to medical treatment and that Professor Polak would need heart/lung transplantation. She was seen by Professor Magdi Yacoub and went home to await the operation.

On 17 July 1995, Professor Polak received a combined heart and lung transplant at Harefield Hospital, with revascularisation of the bronchial artery using the left internal mammary artery. The donor was a 34 year-old woman who died of a subarachnoid haemorrhage. The total ischaemia time was 140 minutes. The presence of cytomegalovirus (CMV) was confirmed in both donor and recipient by serology. Further characterisation of the infection by the polymerase chain reaction (PCR) demonstrated that the donor strain of CMV was different from that present in the recipient (Fig 1). The number of mismatches at the HLA loci were as follows: A:1, B:1 and DR:2. Both the panel reactive antibodies and the lymphocyte specific crossmatch were negative.

Before surgery, Professor Polak received 6 mg/kg of cyclosporin and 4 mg/kg of azathioprine, and 1 g of methylprednisolone in the peri-operative period. Immunosuppression was subsequently maintained with azathioprine (2 mg/kg) and cyclosporin aiming for therapeutic trough levels of 450–550 ng/ml at 1 month, 300–400 ng/ml at 2–3 months and 200–250 ng/ml thereafter.

Professor Polak made very good initial progress. A routine angiogram on the 11th post-operative day showed a patent internal mammary artery. At this stage her FEV₁ was 1.59 l and FVC was 1.72 l. On day 13, she felt very tired, with tightness in the chest and worsening of her respiratory function tests. She was therefore treated for graft rejection with 1 g of methylprednisolone for a period of three days. On day 23, her condition deteriorated when she developed an episode of septicaemia associated with respiratory failure, and she was transferred to ITU. Blood cultures were positive for *Enterococcus faecalis*, *Staphylococcus epidermidis* and *Morganella* spp. A CMV antigenaemia test was also positive. She was therefore treated with intravenous teicoplanin, ampicillin, ofloxacin; ganciclovir for CMV and methylprednisolone for graft rejection. On day 35, both *Aspergillus* and *Candida* spp. were cultured from the sputum, for which she received treatment with itraconazole and fluconazole. On day 60, she had a further episode of CMV infection and required treatment with ganciclovir (Fig 2).

![Fig 1. PCR cytomegalovirus genotyping data (1 = molecular marker, 2 = donor CMV PCR, 3 = recipient pre-operative PCR, 4 = recipient post-operative PCR, 5 = negative control).](image1)

![Fig 2. Lung biopsy showing: a) a focus of interstitial pneumonitis (H&E; magnification ×120), in which there are b) occasional CMV-positive viral inclusions (strepavidin-biotin; magnification ×240).](image2)
As a result of the repeated episodes of rejection, cyclosporin treatment was changed to tacrolimus, which has been shown to be effective as salvage therapy in patients who continue to have repeated rejection episodes with cyclosporin. Following this, Professor Polak made an uneventful recovery (Fig 3). One year after the transplant operation, her FEV₁ and FVC were 2.49 and 2.83 l respectively and these values were maintained on repeat testing at 24 months. A routine right and left heart catheter also performed at one year showed normal coronary arteries in the transplanted heart with no recurrence of pulmonary hypertension: pulmonary artery pressure was 18/7 mm Hg, mean 11 mm Hg, with a pulmonary vascular resistance of 0.95 Wood units. At 24 months her FEV₁ and FVC remained stable; she had a normal ECG during 741 minutes exercise on a treadmill (Bruce protocol). At the time of writing, 28 months after the operation, Professor Polak leads a full professional and family life, visiting the gym daily and attending conferences abroad.

**Pathology (Professor Polak)**

It is a strange irony that I was given the opportunity to study my own lungs and find pathological changes consistent with primary pulmonary hypertension. My work has made me particularly familiar with the pathology of this condition over the years. Following my transplant operation, multiple specimens from both my lungs were sent to the Department of Histopathology at Harefield Hospital (Dr M Burke) and to my department at the Hammersmith Hospital. On macroscopic examination, my pulmonary artery and branches were thickened and atheromatous, and there was subpleural segmental collapse and fibrosis involving the posterior basal segment of my left lower lobe. On microscopic examination, my bronchi showed mild chronic bronchitis and goblet cell hyperplasia of the respiratory epithelium. The basement membrane did not seem unduly thickened. An emphysematous area in my left lower lobe with dilated bronchioles was also found. I also had scar tissue in the posterior basal segment with extensive interstitial fibrosis and dilated bronchioles filled with pus. This was probably the result of the repeated chest infections I had over the years. The extent of bronchial dilatation and the surrounding chronic inflammation suggested early follicular bronchiectasis. I could also see foci of neuroendocrine cell aggregates, so-called ‘tumourlets’ (immuno-reactive to bombesin, a growth promoting regulatory peptide frequently found in neuroendocrine cells of the lung) adjacent to enlarged hypertrophied arteries and bronchioles at the branching points in the scarred area.

The most striking microscopic abnormalities in my lungs were vascular, with a spectrum of changes associated with plexogenic pulmonary arteriopathy. The pulmonary arteries were dilated and showed focal aggregates of foamy macrophages consistent with atheroma deposition. There was muscularisation of the arterioles. I also noted dilatation lesions and abundant plexiform lesions, the latter a hallmark of the end-stage pulmonary hypertension at the bifurcation of smaller arteries. These lesions consist of newly formed vascular channels lined by endothelial cells (Fig 4). As in other cases we recently investigated, these lesions showed a high expression of endothelial nitric oxide synthase (eNOS), whereas a weak and variable staining was seen in all other types of pulmonary vessels. Nitric oxide is
a powerful regulator of lung function, including bronchial and vascular tone, and inhibits platelet aggregation. A deficiency of nitric oxide has recently been postulated to be characteristic of patients with pulmonary hypertension. It is interesting to note that clinically, some patients benefit by the use of nitric oxide as a vasodilatory agent, and histologically a decrease of the endothelial form of the enzyme generating nitric oxide (nitric oxide synthase (eNOS)) has been reported. The significance of these findings remains to be elucidated, but it is possible that high nitric oxide output in plexiform lesions may enhance vasodilation and flow through these structures.

In conclusion, I diagnosed myself to have focal follicular bronchiectasis and neuroendocrine 'tumourlet' formation, but most importantly, I had plexogenic pulmonary arteriopathy, the characteristic feature of pulmonary hypertension, with high expression of endothelial nitric oxide synthase in the plexiform lesions.

**Comment**

Medical therapy for the treatment of primary pulmonary hypertension has met variable degrees of success and no drug treatment has provided a cure for this progressive disease. Prostacyclin is a potent short acting vasodilator that also prevents growth and proliferation of pulmonary arterial smooth muscle cells. In severely symptomatic patients, continuous prostacyclin infusion may improve quality of life and survival. It may be used as a bridge to transplantation or as long-term treatment in those who are unsuitable for transplantation. However, if patients survive, they ultimately require lung transplantation. The long-term survival of patients who have received heart and lung transplantation for primary and secondary pulmonary hypertension is encouraging, with a 1, 5 and 10 year actuarial survival of 60%, 44% and 35% respectively in a survey of 186 patients carried out at Harefield Hospital. Patients achieved an increase in exercise capacity with a VO2 max of 58% at a mean interval of 2 years as well as having a better quality of life as assessed by the Nottingham Health Questionnaire. The major long-term complication of lung transplantation is obliterator bronchiolitis which could respond to enhanced immunosuppression or require retransplantation. The cumulative probability of developing obliterator bronchiolitis was 19%, 53% and 71% at 1, 3 and 5 years respectively.

Patients undergoing heart/lung transplantation at Harefield Hospital are routinely immunosuppressed with cyclosporin, azathioprine and prednisolone in the immediate post-operative period. Following the first month, every attempt is made to withdraw steroid therapy unless the patient has recurrent rejection episodes or is unable to continue on cyclosporin because of deteriorating renal function; or on azathioprine because of a reduction in white cell count. In patients who continue to have recurrent rejection episodes, salvage therapy with tacrolimus (FK506) has been shown to stabilise graft function.

CMV infection continues to be one of the major causes of post-operative mortality and morbidity following heart/lung transplantation. CMV infection occurs in 40–70% of patients within the first three months and tends to be more severe in patients who have primary infection with the virus. Viraemia is routinely detected using the pp65 antigenaemia test and treatment is with intravenous ganciclovir. CMV antigenaemia can easily be quantified, thus providing an estimate of the viral load. This helps in identifying the efficacy of antiviral drug therapy and in the early detection of drug resistance. The monitoring of CMV

**Fig 4.** Photomicrograph of a plexiform lesion in a formalin-fixed, paraffin embedded tissue section (3µm) from a patient with primary pulmonary hypertension. The pan-endothelial cell marker, CD31, illustrates the endothelial cell-lined vascular channels within the lesion (arrow). Immunostaining was performed after autoclave antigen retrieval using the avidin-biotin complex (ABC) method with peroxidase activity revealed with nickel-enhanced diaminobenzidine (magnification x400).
infection is critical for pre-emptive therapy with ganciclovir to prevent CMV disease. The value of the polymerase chain reaction in detecting immediate early viral load and early CMV gene expression is currently under evaluation, as a possible early marker of active CMV infection.

Discussion

Celia M Oakley: I would like to emphasise that primary pulmonary hypertension is a very rare disease and Julia Polak is a leading authority on its pathology. There are only about 100 fatal cases in the UK each year, so the odds against an acknowledged expert in the disease succumbing to it are extremely long. I took part in a case control study involving four European countries—we aimed to get 100 cases, with four controls for each case, to look into the causation of the condition. However, it took us two years to get around 300 cases and only 95 patients were used, largely because of rapid deaths in the new recruits, before the controls could be interviewed. In the US Registry, an average of two years had elapsed between the onset of symptoms and diagnosis. Most patients were originally diagnosed as having asthma or psychological manifestations. This highlights the difficulty in diagnosis, because shortness of breath is the overriding and most important symptom and its causes are manifold. Furthermore, physical signs, ECG and chest radiograph changes develop late in the condition and are not dramatic. Echocardiography clinches the diagnosis immediately if you think of it, but if a cardiovascular cause is not suspected this investigation is not done.

James Scott: What are the causative factors?

Celia M Oakley: The most important connection has been with anorexigenic agents. The initial studies came out of Austria, Switzerland and Germany and showed that anorexigenic fumarate, which is a centrally acting agent, caused primary pulmonary hypertension in some patients who had taken the drug for three months. This is a very small, but real risk. The condition may be reversible in some patients, but this was unfortunately not the case in others.

Colin Dollery: Aminorex fumarate may be associated with an increased risk of primary pulmonary hypertension, but this is less certain with other agents such as fenfluramine, which has been widely used and where the risks are undoubtedly very small.

Celia M Oakley: The association with d-l fenfluramine and dexfenfluramine was highlighted in the rigorously conducted study to which I just alluded. The risk was small, but the association with the administration of this drug is definite and related to duration of use. Professor Polak had taken fenfluramine for more than three months over 20 years ago.

J Michael B Hughes: Is there a pathogenic link?

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Colin Dollery: No one has really explained how aminorex fumarate, fenfluramine or other anorexigenic cause primary pulmonary hypertension. Pathologically, the lungs look exactly like other cases of primary pulmonary hypertension. It is not caused by a pharmacological vasoconstrictive effect.

Celia M Oakley: The patients who developed primary pulmonary hypertension with these agents may have been those who were genetically predisposed to develop the condition, which is sometimes familial. The drug may have acted as a trigger to bring on the disease earlier than otherwise might have been. There was a real epidemic with anorexigen fumarate, although the mechanisms remain unclear.

James Scott: Animal studies and studies on relatives of affected patients indicate that there is a genetic link.

Case Presenters – Julia A Polak, Professor of Histochemistry; Celia M Oakley, Emeritus Professor of Clinical Cardiology; Magdi Yacoub, Professor of Cardiothoracic Surgery; Ghada Mikhail, Registrar in Cardiothoracic Transplantation.

Chairman – James Scott, Professor of Medicine.

Discussion Group – Professor Sir Colin Dollery, Former Dean, Royal-Postgraduate Medical School; J Michael B Hughes, Emeritus Professor of Thoracic Medicine.

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Acknowledgements

We are grateful to Nicola Mason and the late Dr David Springall, Department of Histochemistry, Hammersmith Hospital and Dr M Burke, Consultant Histopathologist, Harefield Hospital for their help with the preparation of this manuscript.

*Editor’s note: This discussion took place before the publication of research that linked valvular heart disease with fenfluramine-phentermine. See: Connolly JH, Gray JI, McGoon MD, Hensrud DD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337:581–8.

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