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Case report

The first heart transplant patient from Northern Ireland

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A 27-year-old bricklayer was admitted to the South Tyrone Hospital, Dungannon, in August 1984. He gave a two-week history of shortness of breath and cough productive of green sputum. He had no chest pain, paroxysmal nocturnal dyspnoea, orthopnoea or peripheral oedema. He was a non-smoker and drank 12 pints of beer per week. He was pyrexial (temperature 99.8°F) and dyspnoeic at rest. He had a cough productive of blood-streaked sputum. The pulse was 132/minute regular. Jugular venous pressure was not raised and the blood pressure was 90/70 mmHg. First and second heart sounds were normal. There was a third heart sound at the apex but no murmurs. In the chest there were coarse and medium crepitations bilaterally in both mid and lower zones.

White cell count was $11,000 \times 10^6$ per litre (73% neutrophils, 27% lymphocytes) and ESR 55 mm in the hour. Chest X-ray showed generalised cardiomegaly and the lung fields showed pulmonary oedema. There were also patchy areas of consolidation throughout the lung fields. ECG showed sinus rhythm, rate 130/minute with a normal axis: PR interval was normal, left ventricular and left atrial hypertrophy were present and there was T wave inversion in V3 to V6. Blood gases showed PO_2 52 mmHg and PCO_2 22 mmHg. Echocardiography showed dilatation of the left atrium and left ventricle with reduced contractility in the posterior wall of the left ventricle. All valves were normal and there was no pericardial effusion. The picture was consistent with dilated cardiomyopathy. Antibodies to coxsackie, adenovirus, cytomegalovirus, psittacosis, Q fever and mycoplasma were not raised. Sputum culture was negative.

The diagnosis was left ventricular failure secondary to dilated cardiomyopathy caused by a possible myocarditis in view of the short history and clinical and echocardiographic findings. There was an associated chest infection.

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Management

He was treated with digoxin, diuretics and vasodilators and warfarin. Despite negative sputum cultures, broad spectrum antibiotics were given and also a short course of high dose steroids. There were runs of self-limiting ventricular tachycardia for which he was started on mexiletine orally.

His condition improved clinically and radiologically and he was gently mobilised. Five days after discontinuing corticosteroids he became acutely breathless and developed a mitral regurgitant murmur with a cough productive of frothy sputum indicating left ventricular failure. Prednisolone was recommenced (60 mg daily), the diuretics continued and within 24 hours there was clinical and radiological improvement. He remained stable for the next four weeks and was discharged home. Over the next three months he required three further admissions for treatment of left ventricular failure.

In December 1984 he was transferred to the Royal Victoria Hospital for further investigation. Cardiac catheterisation and myocardial biopsy were performed and the results of cardiac catheterisation are shown in the Table. Endomyocardial biopsy examination by light and electron microscopy showed the features of a cardiomyopathy. The myocardial fibres were in disarray with a variation in fibre diameter; there was considerable variation in nuclear size, and mitochondrial aggregates were found within the interstitium. There was no inflammation, fibrosis or amyloid deposits. There were no features present on which to make an aetiological diagnosis.

TABLE

Cardiac catheterisation data

Site	*Pressure (mmHg)*	
Right atrium	a	21
	v	17
	mean	14
Right ventricle	Systolic	53
	End diastolic	10
Pulmonary artery		49/31
Pulmonary wedge	a	32
	v	39
Left ventricle	Systolic	89
	End diastolic	32
Aorta		89/61
Left ventricular ejection fraction		13%

Angiography

Left ventricle: Markedly enlarged. Contraction very poor, all wall movements uniformly reduced. Some mitral regurgitation into enlarged left atrium

Right ventricle: Markedly enlarged and contracted poorly. Marked tricuspid regurgitation present.

Conclusion: Congestive cardiomyopathy.

His subsequent course was one of progressive congestive heart failure despite digoxin, intensive diuretic and vasodilator therapy. He required inotropic support (intravenous dobutamine infusion) and despite these measures his cardiac function continued to deteriorate. Progressive hyponatraemia and uraemia developed. The only chance for survival appeared to be cardiac transplantation and he was transferred to Papworth Hospital, Cambridge, in February 1985 for assessment for transplantation. As he was so ill from a low cardiac output state a 'red alert' was circulated for a donor heart. A suitable donor became available on 22 February 1985.

Operative and Post-Operative Course (Papworth Hospital, Cambridge)

The donor heart was implanted and defibrillated from ventricular fibrillation into sinus rhythm. This was followed by a short period of complete heart block. Isoprenaline infusion was maintained for five days and atrial pacing continued for 14 days. On stopping the atrial pacing, the heart maintained normal sinus rhythm at a rate of 75 to 80 per minute.

Pre-operatively he was given cyclosporin A and azathioprine, but because of deterioration in renal function post-operatively cyclosporin A was discontinued and he was maintained on azathioprine. He received corticosteroids at first intravenously and then orally until day 10 when the steroids were stopped and cyclosporin A recommenced. The azathiaprine was continued. There were no rejection episodes in the first two months.

As renal function had deteriorated prior to operation, he had to be dialysed whilst on cardiopulmonary bypass. Post-operatively he again had deteriorating renal function necessitating change in his immunosuppressive therapy. On day 10 his renal function started to improve and on discharge his blood urea was 9.7 mmol/l. He was transferred from the intensive care unit to the general ward on day 17 post-operatively. He had a gradual convalescence and was discharged from hospital on the 54th post-operative day. He returned home and has continued convalescence there without complication. His cardiac function is now Grade I (New York Heart Association).

Pathology of the Resected Heart

The heart weighed 405 gm. All four valves were normal. Both ventricles were dilated, the right ventricle measuring $5 \times 3 \times 8$ cm and the left ventricle measuring 7×8 cm. The coronary arteries were normal. Microscopically there were wavy myocytes and there was moderate hypertrophy of the myocytes in the left ventricle. In the left ventricle there were some areas of contraction bands and two foci of lymphocytic and eosinophilic infiltration in the lateral and septal walls. There was no fibrosis or amyloid present. The findings were consistent with a congestive cardiomyopathy.

DISCUSSION

The first human-to-human heart transplantation was performed in Cape Town in December 1967.[1] Since then, several hundred patients have undergone cardiac transplantation in 22 countries throughout the world, the largest centre being at Stanford, California. The primary indication for cardiac transplantation is severe cardiac failure unresponsive to conventional therapy and due to irreversible disease of the myocardium of the left ventricle. The patient should be 15 to 50

years with a stable social and psychiatric background, with no active or chronic chest infection and no insulin-dependent diabetes or recent pulmonary infarction.

The donor should be between the ages of 15 and 35 years, with no history of cardiac disease, systemic infection or extracranial malignancy. All donor hearts used in the Papworth programme have been removed at the referring hospital by a surgical team from the transplant unit. The diagnosis of brain death in the donor and the maintenance of ventilation and haemodynamic stability of the donor patients are the responsibility of the referring clinicians. The donor heart is removed, rapidly cooled and stored in cold cardioplegic solution at 2-4°C and transported to Papworth, the desirable upper limit of transit being four hours.[2] During the five-year period January 1979 to December 1983, 62 hearts were used from a total of 250 offers.[2] Seventy-seven were rejected on medical criteria, and 80 hearts were not used because of insufficient local facilities.

The recipient is placed on cardiopulmonary bypass. For orthotopic transplantation as in our patient the heart is excised leaving the posterior walls of both atria and their venous connections in situ. The aorta and pulmonary artery are divided immediately distal to the aortic and pulmonary valves. The donor atria (including the sino-atrial node) are sutured to the corresponding structures in the recipient,[3] as are the aorta and pulmonary artery.

Heterotopic transplantation as performed by Barnard since 1974 now involves biventricular bypass, with anastomoses between recipient and donor right atriae, left atriae, aortae and pulmonary arteries. Heterotopic transplantation carries the potential advantage of leaving in situ the recipient's own right ventricle which is often healthy or may be hypertrophied in response to raised pulmonary resistance. The recipient's own heart may also provide support for the circulation while the donor heart function is compromised by transit-induced ischaemia or acute rejection. The overall survival rates at one, two and three years for heterotopic transplantation were 64%, 50% and 40% respectively.[1]

Rejection is most frequent in the first three months with an average frequency during this time of one episode per 22 patient days, decreasing to one episode per 325 patient days after the first year.[3] The aim is now to detect activation of the immune response system by immunological monitoring using sheep red cell rosette formation and endocardial biopsy before rejection has become established.[4, 5] Chronic rejection is an insidious process which obliterates the donor coronary arteries, and is assessed by annual coronary angiography. The incidence of graft arteriosclerosis at Stanford has improved since the introduction of anti-thrombotic agents, with a graft arteriosclerosis rate of 35% in five years.[4] Seventeen out of 27 patients transplanted at Papworth from 1977 to 1981 were alive at the end of 1981,[3] and 50 out of 94 patients operated on at Stanford between 1973 and 1978 survived four years.[4] In terms of quality of life, 90% of patients transplanted at Stanford up to August 1976 and surviving three months post-transplantation returned to New York Heart Association Grade I. The development of malignant neoplasms in transplant recipients has been recognised since 1968,[6] particularly among those with renal transplants. During the follow-up of 141 patients with heart transplants from Stanford between 1968 and 1977 malignant neoplasms developed in 11 patients. The time interval from transplantation to diagnosis of malignancy ranged from 135 days to 78 months.

At 1982 prices the estimated cost per patient transplanted at Papworth, including pre-operative assessment and first year post-operative follow-up is of the order of

£15,000.[3] The major component of this bill is the cost of post-operative surveillance for rejection and infection. If an immunosuppressive 'magic bullet' were available — effective but non-toxic — the cost of heart transplantation could be reduced to little more than the cost of routine open heart surgery. From 1979 to 1983, 40% of patients selected for transplantation died whilst waiting for a heart to become available.[2] An adequate supply of donor hearts requires awareness by intensive care clinicians that the need exists, and their willingness to ask for the organ to be donated. Out of a total of 250 offers concerning cardiac donation, only on 19 occasions was consent withheld by relatives,[2] and many hearts were offered by relatives agreeing to donation of kidneys, and then asking if other organs could also be donated. Transplant teams acknowledge the difficulty in asking distressed relatives for permission to transplant organs, but feel justified by the benefit which other patients stand to gain.

Human cardiac transplantation, either orthotopic or heterotopic, has been performed in several hundred patients in 22 centres throughout the world. It offers an increase in survival and improved quality of life to those with terminal cardiac failure for whom conventional therapies are ineffective. So far two patients from this province, both with congestive cardiomyopathy, have had successful transplants. Success of the procedure depends on an awareness among clinicians throughout the country — both that such a facility exists for suitable patients, and that a demand exists for a steady supply of suitable donor hearts.

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