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BRIEF REPORT

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Heart transplantation for radiation-associated end-stage heart failure

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Abstract Radiation-induced heart disease is an increasingly recognized late sequela of mediastinal radiation therapy for malignant neoplasms. We report four cases of heart transplantation for end-stage heart failure induced by mediastinal radiation therapy. Short-term and intermediate-term results are excellent with all four patients currently surviving a mean of 48 months after transplantation. Neither a second malignancy nor recurrence of the primary malignancy has been observed to date. The early results of heart transplantation for end-stage, radiation-induced heart disease are encouraging.

Key words Radiation-induced heart disease · Heart transplantation

Abbreviations FEV_1 Forced expiratory ventilation at 1 s · *FVC* Functional vital capacity · *MRT* Mediastinal radiation therapy · *NYHA* New York Heart Association · *PVR* Pulmonary vascular resistance

Introduction

Mediastinal radiation therapy (MRT) for malignant neoplasms such as Hodgkin's disease and breast cancer achieves an increasing number of long-term survivors [5, 16]. However, heart disease associated with MRT is a significant cause of late morbidity and mortality [2, 6, 11, 13, 15]. In Hodgkin's disease, heart disease is the second-most common cause of late death [6]. A range of findings can characterize the pathophysiology of the late effects of MRT on the heart: pericardial disease, conduction disturbance, myocardial fibrosis, valvular heart disease, and coronary artery disease [1]. Surgical treatment by pericardiectomy, coronary artery bypass surgery, and valvular heart surgery has been reported in this patient population [3, 8, 10, 12, 14]. Although these surgical treatments are effective, the progressive nature of radiation-induced cardiac damage can result in ongoing myocardial dysfunction, leading to the development of end-stage heart failure. In this report, we present four cases of heart transplantation for end-stage heart failure induced by MRT.

Materials and methods

Recipients of heart transplantation who had a history of MRT for malignant neoplasm were gleaned from the transplant database at Mayo Clinic. A total of four recipients was identified. For this study, operative notes, anesthesia records, clinical case histories, and laboratory investigations (including pulmonary function tests, echocardiography, cardiac catheterization data, and radiation oncology records) were reviewed retrospectively. Follow-up data

Table 1 Pretransplant data (*Pt* Patient, *MRT* mediastinal radiation therapy, *NHL* non-Hodgkin's lymphoma, *HL* Hodgkin's lymphoma, *EF* ejection fraction, *S/P CABG* status post coronary artery bypass grafting, *MR* mitral regurgitation, *TR* tricuspid regurgitation, *AS* aortic stenosis, *S/P MVR* status post mitral valve replacement, *S/P TVR* status post tricuspid valve repair, *NYHA* New York Heart Association, *2VCAD* two vessel coronary artery disease)

Pt	Sex	Malignancy	Chemotherapy	Age at MRT and transplantation (years)	EF (%)	Heart disease (NYHA class II/IV)
1	M	NHL	(+)	29 : 42	15	MR (NYHA class II/IV), TR (NYHA class III/IV) S/P CABG × 3/all grafts patient
2	M	NHL	(−)	34 : 61	15	MR (NYHA class III/IV)
3	M	HL	(−)	24 : 50	20	Mild AS, MR (NYHA class III/IV) 2VCAD
4	M	HL	(+)	10 : 29	15	S/P MVR + S/P TVR

Table 2 Pretransplantation right heart catheterization data (*Pt* Patient, *RAP* right atrial pressure, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *TPG* transpulmonary pressure gradient, *PVR* pulmonary vascular resistance (Wood unit), *PVRI* pulmonary vascular resistance index, *AOP* aortic pressure, *CO/CI* cardiac output/cardiac index)

Pt		RAP	PAP	PCWP	TPG	CO/CI	PVR	PVRI	AOP
1	Baseline	38	106/58 (73)	53	20	3.3/1.6	6.1	12.5	143/101 (114)
	Nitroprusside		69/38 (51)	37	14	7.6/3.7	1.8	3.8	92/56 (69)
2	Baseline	3	27/19 (23)	16	7	4.5/2.5	1.6	2.8	82/51 (63)
	Nitroprusside								
3	Baseline	13	49/28 (36)	24	12	3.5/1.8	3.4	6.6	85/61 (70)
	Nitroprusside		43/23 (32)	20	12	4.6/2.4	2.6	5.1	77/53 (62)
4	Baseline	10	43/14 (26)	14	12	4.0/2.3	3.0	5.2	96/51 (65)
	Nitroprusside		22/9 (16)	11	5	5.1/3.0	1.0	1.7	85/41 (53)

were collected from outpatient records focusing on functional status, echocardiography, results of endomyocardial biopsies, and the presence or absence of new or recurrent malignancy.

The oncology treatment history and preoperative cardiac status, as assessed by echocardiography and coronary angiography, are detailed in Table 1. The mean age at MRT was 24.3 ± 10.3 years (range 10–34 years). The mean age at heart transplantation was 45.5 ± 13.5 years (range 29–61 years). The mean interval between MRT and heart transplantation was 21.3 ± 6.6 years (range 13–27 years). Two patients had concomitant chemotherapy including Adriamycin. Patient 3 also had a second malignancy (osteosarcoma in the scapula), which was treated surgically 15 years after the original MRT. All patients presented with New York Heart Association (NYHA) class IV symptoms despite maximal medical therapy. Pretransplant cardiac catheterization data and pulmonary function tests are detailed in Tables 2 and 3. Of note, one patient had severe pulmonary hypertension, and two patients had moderate pulmonary hypertension. A mild-to-severe restrictive pattern and mild obstructive pattern on pulmonary function testing were observed in all patients.

Results

All four patients underwent standard orthotopic heart transplantation with biatrial anastomosis. Perioperative immunosuppressive therapy consisted of low-dose OKT3 induction therapy followed by a triple drug regimen of cyclosporine, azathioprine, and prednisone. In patient 1, femoral arterial cannulation was used, and dense adhesions were dissected after cardiopulmonary bypass was instituted. The postoperative course in patient 1 was complicated by donor right heart failure, requiring prostacyclin (PGI_2) infusion, prolonged ventilatory support, and hemodialysis for 4 days. In this patient, immunosuppressive therapy was modified using prolonged OKT3 monotherapy for 31 days, followed by a triple drug regimen with cyclosporine, azathioprine, and prednisone. The patient slowly recovered and was discharged well on day 110 after transplantation. The other three patients had uneventful postoperative courses. Mean patient follow-up is 48.0 ± 34.0 months (range 15.5–83 months). Patient 3 developed liver dysfunction associated with azathioprine, requiring a switch to mycophenolate mofetil. At most recent follow-up (Table 4), two recipients had been weaned from steroids. NYHA functional class at most recent follow-up was I in all patients. No second malignancy was observed at this time after heart transplantation. Postoperative pulmonary function tests were available only for patients 2 and 4. In patient 2, the forced expiratory ventilation at 1 s(FEV_1) in liters

Table 3 Pretransplantation pulmonary function data (*Pt* Patient, *FVC* functional vital capacity, *FEV_1* forced expiratory ventilation at 1 s)

Pt	FVC (l)	% FVC predicted value	FEV_1 (l)	% FEV_1 predicted value	FEV_1/FVC (%)
1	2.07	38	1.51	35	75
2	3.00	75	2.08	65	69
3	3.85	78	2.60	66	68
4	2.10	46	1.81	47	86

and % predicted increased from 2.08 to 2.39 and 65% to 73%, respectively, measured at 3 weeks after transplantation. FEV_1/functional vital capacity(FVC)(%) increased from 69% to 75.6%. In patient 4, the FEV_1 in liters and % predicted fell from 2.10 to 1.36 and 47% to 32%, respectively, again measured 3 weeks after transplantation. FEV_1/FVC(%) increased from 86% to 89%. These measurements were taken in the presence of significant pleural effusions, which were later drained. Table 4 shows the number of infection and rejection episodes in the first year after transplantation. In the overall program ($n = 166$), the 1-year actuarial (Kaplan-Meier) freedom from infection and rejection is 37.3 ± 4.1% and 31.1 ± 3.9%, respectively. The overall program 1- and 5-year actuarial patient survival is 94.4 ± 1.9% and 83.2 ± 3.4%, respectively (Kaplan-Meier).

Discussion

The present study suggests that previous malignancy and MRT are not contraindications for heart transplantation. With advances of radiation oncology over the last 2 decades, there is an increasing number of long-term survivors after MRT for malignant neoplasm. Heart disease is the second-most common cause of late death after MRT for Hodgkin's disease [6]. Radiation therapy can be a treatment modality for breast cancer, thymoma, esophageal cancer, seminoma, and lung cancer [1]. The effects of MRT on the heart include pericardial disease including constrictive pericarditis, conduction disturbance, coronary artery disease, valvular heart disease, and myocardial fibrosis with heart dysfunction [1]. In addition to the sequelae involving the heart, pulmonary parenchymal disease, esophageal stricture, carotid stenosis, and hypothyroidism have been reported [8]. Scar formation or skin changes in the anterior chest can also be a side effect of radiation, predisposing to mediastinal wound complications [8].

Conventional surgical management for these patients such as coronary bypass surgery and/or valvular heart surgery have been reported [3, 8, 10, 12, 14]. One recent study regarding coronary bypass grafting after MRT demonstrated good short-term results, but intermediate results were limited by a recurrent malignancy and/or heart failure [8]. In this study, of the 17 late deaths out of a total of 47 patients studied, the largest number (7 deaths) were due to malignancy, 2 to recurrences of the previous neoplasm, and 5 to new malignancies. In a further study of valvular heart surgery in 60 patients with MRT, of 19 late deaths, malignancy was the most common cause occurring in 7 patients (N. Handa et al., submitted for publication). This study also showed that preoperative comorbidities such as carotid disease and pulmonary parenchymal disease were common [8]. Myocardial fibrosis with cardiac dysfunction is a serious complication of MRT. In general, the radiation effect is progressive and continuous. Progressive deterioration of heart function and the development of end-stage heart failure have been observed after MRT, even after initially successful management with conventional open heart surgery for valvular or coronary artery disease. Concomitant pericardial disease or pulmonary hypertension associated with pulmonary parenchymal disease may exacerbate symptoms of heart failure. Heart transplantation is an option for those patients with severe symptoms of end-stage heart failure; however, a number of factors must be considered before heart transplantation is undertaken. Careful evaluation before transplantation is required, particularly as it relates to pulmonary function, pulmonary vascular resistance, and malignant status. It is mandatory to confirm that the primary malignancy has been cured or is in complete remission [4, 10]. Several studies describe the increased incidence of a second malignancy; this was observed in patient 3 in the present report [17]. Preoperative comorbidities resulting from previous MRT, in particular, pulmonary parenchymal disease with an increased pulmonary vascular resistance (PVR), can exclude patients

Table 4 Follow-up status (*Pt* Patient, *NYHA* New York Heart Association, *CyA* cyclosporin A, *AZA* azathioprine, *PDS* prednisone, *MMF* mycophenolate mofetil)

Pt	Follow-up term (months)	NYHA class at follow-up	Maintenance immunosuppression	Working status	No. of infection episodes in 1st year	No. of rejection episodes in 1st year
1	83	I	CyA, AZA, PDS	Full-time	3	1
2	71	I	CyA, AZA, PDS	Retired, active	2	1
3	22	I	CyA, AZA, PDS	Full-time	1	0
4	15.5	I	CyA, MMF, PDS	Full-time	0	0

from transplantation [4, 10]. In patient 1, a high PVR was present, which resulted in perioperative donor right heart failure, unresponsive to isoproterenol and nitroprusside, but responsive to prostacyclin (PGI_2) infusion. Although the postoperative course was complicated, this patient is working full-time with good functional status 6 years after heart transplantation.

MRT may affect the immunological response of the recipient. Although two of the four patients underwent previous open heart surgery as well as MRT, no mediastinal complications occurred, which is consistent with a previous report [7]. Three of four patients who underwent MRT suffered at least one episode of infection in the first year after transplantation, and two of four patients had one episode of rejection, suggesting a degree of persisting immunosuppression from MRT, although the number of cases is too small to compare statistically to the overall patient population. Post-transplant immunosuppressive therapy may also increase the risk of developing a second malignancy.

In conclusion, we present four cases of successful heart transplantation for end-stage heart failure induced by MRT. Careful assessment of preoperative comorbidities and intraoperative risk is required for appropriate selection of heart-transplant candidates with previous malignancy and thoracic radiation.

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