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Primary bronchogenic carcinoma in recipients of heart transplants

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Abstract With the exception of carcinomas of the skin and lip, carcinoma of the bronchus is the most common carcinoma that afflicts recipients of solid organ grafts. Of 859 tumors occurring in 830 recipients of thoracic organs reported to the Cincinnati Tumor Transplant Registry, 242 were carcinomas and 68 of these were bronchogenic carcinomas, which therefore made up 8 % of the overall total. There are, however, relatively few reports of heart transplant patients with bronchogenic carcinoma in the literature. We present details of four patients who developed this malignancy out of a total of 196 patients who survived and have been followed up for more than 3 months at our center, an incidence of 2 %. The mean period from the time of transplant to diagnosis of malignancy was 58 months (range 11–82 months). The histology was squamous or anaplastic in three cases, and adenocarcinoma in one. Immunosuppressive therapy was reduced in all cases. Resection was carried out in two patients (both of whom died 6 and 11 months later, respectively), resection was combined with chemotherapy and radiation in one patient (alive 15 months later), and therapy consisting of radiation alone was given to one patient (died within 1 month). We conclude that bronchogenic carcinoma is relatively common in patients with heart transplants and that it has a poor prognosis.

Key words Bronchogenic carcinoma, heart transplantation · Heart transplantation, bronchogenic carcinoma · Immunosuppression, bronchogenic carcinoma

Introduction

It is well known that organ transplant recipients have a high incidence of de novo malignancy when compared with the general population [13]. The incidence increases with the length of follow-up after organ transplantation [15]. This is believed to be the result of long-term pharmacological immunosuppressive therapy. However, the majority of neoplasms that are observed frequently in the general population (carcinomas of the bronchus, breast, prostate, and colon, and invasive uterine cervical carcinomas) show no increased incidence in transplant patients [10–13, 15]. In fact, only two varieties of cancer often observed in the general population are encountered in significantly increased numbers in transplant patients, these being squamous cell carcinomas of the skin and in situ carcinoma of the uterine cervix. In contrast, a variety of malignancies that are uncommon in the general population are commonly seen in transplant patients, including lymphomas, lip cancer, Kaposi's sarcoma, carcinoma of the kidney, carcinoma of the vulva and perineum, hepatobiliary tumors, and other sarcomas [10–13, 15].

Although carcinoma of the bronchus is reportedly no more common in patients with heart transplants than in the general population, it does account for the highest

number of tumors in recipients of thoracic organs, with the exception of cancers of the skin and lip and lymphomas (Table 1). The Cincinnati Transplant Tumor Registry has data on 8191 patients who developed 8724 cancers de novo after transplantation [10–13, 15]. Of these patients, 772 received heart, 29 combined heart-lung, and 29 lung allografts. Of 859 tumors occurring in 830 recipients of thoracic organs, 68 were in the lung, accounting for 8 % of tumors and 28 % of carcinomas (Table 1). The equivalent numbers in relation to renal transplant recipients are 406 out of a total of 7318 tumors (5.5 %), accounting for only 13 % of carcinomas [13].

Although there is a relatively high incidence of primary bronchogenic carcinoma in recipients of heart transplants, there are surprisingly few reports of its management in the literature [2, 3, 17]. However, two recent surveys at major transplant centers have added significant data [4, 14]. At our own center, 221 heart transplants have been performed in 215 patients since 1985, and 4 of these patients have developed de novo bronchogenic carcinoma. Sixteen of these 215 patients died within the first 3 months (7.4 %) and 3 patients have as yet not been followed up for a minimum of 3 months. Of those at risk for carcinoma (having been followed for more than 3 months), the incidence of de novo lung cancer has been 2 %.

Here we present a brief history of the four patients who developed primary bronchogenic carcinoma, and we discuss potential risk factors and management options.

Table 1 De novo malignant disease in thoracic organ transplant recipients[a,b]

Type of malignant disease	Number of tumors in thoracic organ transplant recipients
1. Lymphomas	339
2. Cancers of skin and lip	239
3. Kaposi's sarcoma	19
4. Sarcomas (excluding Kaposi's)	10
5. Leukemias	10
6. Carcinomas:	
Bronchus	68
Prostate	28
Colon and rectum	18
Head and neck (excluding thyroid, parathyroid, and eye)	18
Kidney	16
Breast	9
Hepatobiliary	9
Metastatic (primary site unknown)	8
Pancreas	8
Uterine cervix	7
Urinary bladder	7
Vulva, perineum, penis, or scrotum	6
Thyroid gland	6
Stomach	5
Testis	4
Ovary	1
Miscellaneous	24
Total	859

[a] One cardiac transplant recipient had three separate types of neoplasm, and 26 others had two each. One pulmonary recipient had two tumors

[b] Modified from I. Penn [13]

Clinical histories

Details of the four patients are provided in Table 2. Their ages at the time of heart transplantation (HTx) ranged from 40–58 (mean 50) years, and at the time of presentation of carcinoma of the bronchus from 47 to 63 (mean 55) years. Two patients were male and two female. Patients 1 and 2 underwent HTx at a time when our immunosuppressive program included routine induction therapy with antithymocyte globulin, followed by maintenance triple immunosuppressive therapy with cyclosporin, azathioprine, and low-dose prednisone. Patients 3 and 4 received only cyclosporin, azathioprine, and high-dose prednisone with no induction therapy. Details of these regimens have been presented previously [5, 6]. The underlying condition for which HTx was performed was ischemic cardiomyopathy in three patients and idiopathic dilated cardiomyopathy in one patient (patient 4). All four patients had a long history of smoking ranging from 20 to 120 pack-years (mean 80 pack-years), but all claimed to have discontinued smoking after HTx. Symptoms of bronchogenic carcinoma presented between 11 and 82 months after HTx (mean 58 months).

In all patients, once the diagnosis of malignant disease had been made, attempts were made to reduce immunosuppressive therapy. This included (1) reduction of cyclosporin to a whole blood trough level below 100 ng/ml, (2) discontinuation of azathioprine, and (3) discontinuation or reduction of prednisone to less than 5 mg/day. This decision was based on anecdotal opinion and experience with other types of cancer in immunosuppressed patients [18] that suggested that reduced immunosuppression might slow the growth and spread of tumor. A substantial reduction in immunosuppressive therapy was achieved in two patients (patients 1 and 3).

Further details of the courses of these four patients are given below.

Patient 1

This patient underwent HTx in 1988 but developed chronic renal failure from cyclosporin nephrotoxicity, necessitating chronic dialysis and subsequent kidney transplantation in 1991. In 1995, chest radiography and a CT scan revealed a mass in the right upper lobe, which was shown by bronchoscopic biopsy to be an adenocarcinoma. Right upper and middle lobectomies were performed, but the operation was considered noncurative due to histopathological involvement of hilar and mediastinal lymph nodes. The patient survived only 6 months.

Table 2 Clinical data of four patients who developed bronchogenic carcinoma (CA) after heart transplantation (HTx)

Patient (Sex)	Smoking history Packs per day/years	Age (years) at HTx/at diagnosis of CA	Interval between HTx and CA (months)	Histopathology of tumor	Staging of tumor	Treatment	Outcome	Interval between CA and death or date last seen (months)
1 (F)	1/20	40/47	82	Adeno	IIIa	Right upper and middle lobectomies	Dead	6
2 (F)	2/30	57/63	79	Squamous	IIIa	Radiation	Dead	< 1
3 (M)	4/30	45/51	60	Anaplastic small cell	I	Right upper and middle lobectomies, chemotherapy, radiation	Alive	15
4 (M)	3/40	58/59	11	Squamous (bilateral)	IV	Left lower lobectomy and wedge resection of right lower lobe	Dead	11

Patient 2

Six and one-half years after HTx, this patient presented with pneumonia that was found to be related to the presence of a poorly differentiated squamous cell carcinoma of the lower lobe of the right lung. Investigation revealed the presence of mediastinal lymph node involvement, eliminating the possibility of cure by operation. The patient underwent a course of radiation therapy to the mediastinum but died within 1 month.

Patient 3

Five years after HTx, chest radiography and CT scan revealed a mass of approximately 3 cm diameter in the right middle lobe, with no mediastinal adenopathy. Bronchoscopy and biopsy were not diagnostic and so the patient underwent thoracotomy with right upper and middle lobectomies. Histopathology showed anaplastic small cell carcinoma. The patient subsequently received a course of chemotherapy, followed by radiation therapy to the mediastinum. He remains well 15 months after the lobectomy.

Patient 4

Eleven months post-HTx, this patient developed chest radiographic and CT scan appearances of bilateral lung masses. Fine needle aspiration showed poorly differentiated squamous cell carcinoma with extensive tumor necrosis. A left lower lobectomy and a wedge resection of the right lower lobe mass were performed during two different operative procedures. Although his initial recovery was good, some 8 months later he presented with liver and bone (ribs) metastases and he died within 3 months.

Discussion

Some of the earliest reports of malignant neoplasms occurring in patients with cardiac transplants were from Stanford [1, 7, 16] and Cape Town [8]. The incidence of bronchogenic carcinoma in HTx recipients is uncertain but would seem to be between 0.7 % and 2.0 %. The Papworth group has reported 2 cases out of 275 patients (0.7 %) [2], the St. Louis University group 3 out of 196 patients (1.5 %) [3], Pittsburgh 10 out of 608 (1.6 %) [14], and Columbia 5 out of 633 (0.8 %) [4]. In our own series, the incidence in patients followed for more than 3 months is, to date, 2 %. The incidence in the general population is estimated to be approximately 0.07 % [9]. Pham et al. [14] have suggested that there may be a 25-fold increase in lung cancer in HTx recipients.

Although these figures might suggest an increased incidence of bronchogenic carcinoma in patients with HTx, this may well be related to the fact that HTx recipients are a selected group with a higher than average risk profile for lung cancer. Indeed, the possibility exists that neoplastic change was already present in the lung at the time of HTx, though clearly undetectable at that time. Whether the incidence is indeed higher than in the general population can only be confirmed by comparison with a group matched for such factors as age, sex distribution, and exposure to tobacco.

Fleming et al. [3] have suggested a number of factors that could contribute to the relatively high incidence of lung cancer in patients who have undergone HTx. These include (1) a heavy smoking history, which is common in patients with ischemic heart disease; (2) relatively advanced age, as most of these patients are in their 50s and 60s, which is an age where the incidence of lung cancer begins to rise dramatically in the general population; and (3) immunosuppression. A heavy smoking history is probably the most important factor and has been emphasized by both Pham et al. [14] and Goldstein et al. [4].

Yokoyama et al. [18] have described an accelerated growth rate of hepatocellular carcinomas in immunosuppressed patients, and it has been suggested that rapid tumor growth in patients with a compromised immune system makes it difficult to detect cancers at an early stage. In this respect, it is perhaps worth noting that in

three of our four patients, the tumors were at an advanced stage at the time of presentation. This has also been the case in the reports from Pittsburgh [14] and Columbia [4], where eight out of ten and five out of five, respectively, were at an advanced stage when first diagnosed. Resection was possible in only three of ten patients in the Pittsburgh series and in none in the Columbia series.

It is clearly disturbing that so many cases are diagnosed at such a late stage. It would, therefore, seem essential to maintain a high level of surveillance for any sign of malignant disease in HTx patients, particularly those with a smoking history, and to investigate any suspicious signs as urgently as possible. However, even with chest radiography every 6 months, the Pittsburgh group failed to diagnose bronchogenic carcinoma until it was advanced in seven of ten cases [14]. Chest radiography may, therefore, be required even more frequently if such carcinomas are to be identified at an early stage. However, whether early identification will result in improved survival remains uncertain.

When there are clinical features suggestive of bronchogenic carcinoma in a patient with a thoracic organ transplant, the progression of the disease would clearly appear to be rapid. Three of the four patients at our own center died within 14 months, and eight of ten at Pittsburgh [14] and all five of the Columbia patients [4] died within the same period of time. It is therefore important to investigate and make the diagnosis as soon as possible. The patient's best chance of survival is if (1) investigation to exclude distant metastases is made urgently, and (2) curative surgical resection is performed whenever possible. A case can be put forward to minimize immunosuppressive therapy although there is no evidence that such a reduction would reduce the progression of bronchogenic carcinoma in HTx patients. Furthermore, this might put the patient at risk of rejection. In the present series, immunosuppression was reduced significantly in Patients 1 and 3 (one of whom, with a small cell tumor, is the only patient who remains alive) without the development of acute rejection.

The optimum therapy for malignant disease in immunosuppressed patients would appear to be multimodal, possibly involving (1) a decrease in, or cessation of, immunosuppression, (2) excision, (3) chemotherapy, (4) radiotherapy and, in relevant cases, treatment with (5) antiviral agents such as acyclovir, ganciclovir, or interferon, or with (6) monoclonal anti-B-cell antibodies [1]. Not all of these therapeutic modalities, however, would be possible or helpful in patients with bronchogenic carcinoma.

Resection of lung cancers in patients who have undergone previous HTx would appear to be possible without undue risk. With the exclusion of atrial dysrhythmias, none of the three patients who underwent lobar resections in the present series developed any major postoperative complications.

Data regarding malignant disease in patients with lung transplants are exceedingly few; yet, one can anticipate a high incidence of bronchogenic carcinoma in the future in patients who undergo lung transplantation for emphysema, many of whom have a long smoking history. Indeed, in our small series of only 20 lung transplants, we have recently seen bronchogenic carcinoma in the native lung of one patient approximately $4^1/_2$ years after single lung transplantation for emphysema.

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