Cause of Death and Sudden Cardiac Death After Heart Transplantation

An Autopsy Study

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Key Words: Autopsy; Cardiac transplantation; Rejection; Coronary atherosclerosis; Fibrointimal hyperplasia

Abstract

Postmortem findings in 39 patients following cardiac transplantation are presented. Causes of death were right-sided heart failure after transplantation (6 [15%]), infection (5 [13%]), multisystem organ failure (4 [10%]), complications of noncardiac surgery (3 [8%]), acute rejection (3 [8%]), malignant neoplasm (3 [8%]), graft vascular disease (3 [8%]), preservation procurement injury (3 [8%]), cardiac arrhythmia (2 [5%]), other (4 [10%]), and unclear (3 [8%]). Seven patients in medically stable condition died after a sudden cardiac arrest, and these constituted 27% (7/26) of deaths more than 1 month after transplant. The 7 sudden cardiac arrests were due to graft vascular disease (2 [29%]), acute rejection (2 [29%]), cardiac arrhythmias (2 [29%]), and hyperkalemia during an exacerbation of acute renal failure (1 [14%]). In 3 of the 5 patients who died of sudden cardiac arrest not due to acute rejection, hemodialysis and plasmapheresis were triggers of the event. Pulmonary hypertensive arteriopathy was associated with early death and rightsided heart failure, and 6 of 8 patients with these changes died perioperatively or postoperatively.

Orthotopic heart transplantation is a well-established procedure to prolong the life of patients with severe cardiomyopathy due to a variety of causes. More than 57,000 heart transplants had been reported to the Registry of the International Society for Heart and Lung Transplantation through the year 2000. Although substantial data have been reported as to the cause of death in these patients, most autopsy-based studies are at least a decade old. Few new autopsy data have been presented since McManus highlighted the pressing need for these types of studies to better understand allograft pathology, transplant arteriopathy, and the spectrum of disease present in heart transplant recipients. We reviewed the autopsy reports and clinical records of cardiac transplant recipients during a 16-year interval to determine the cause of death. A subgroup of patients who died of sudden cardiac arrest is discussed in detail.

Materials and Methods

From 1985 to 2001, 325 orthotopic heart transplants were performed at Duke University Medical Center (DUMC), Durham, NC. Of the 325 patients, 97 died and 39 were autopsied, for an autopsy rate of 40%. Only patients who had received their first heart transplant were included in the study. Two of the autopsied patients underwent cardiac transplantation at other medical institutions but were receiving care at DUMC when they died. The types of autopsies completed were full in 25 cases (64%), limited to the heart and lungs in 5 (13%), heart only in 5 (13%), chest and abdomen only in 3 (8%), and abdomen only in 1 (3%).
The cause of death was determined by a review of the clinical and autopsy records. Only the primary event that led directly to death or resulted in clinical deterioration of the patient’s condition culminating in death was deemed the cause of death. The cause of death was stratified based on survival time: 0 to 1 month, 1 month to 2 years, and greater than 2 years. A subgroup of patients who were in medically stable condition and then died after a sudden cardiac arrest are discussed in detail by correlating their clinical history and postmortem cardiac pathology. Severely ill hospitalized patients who died of a cardiac arrest are not included in this discussion.

The amount of coronary artery disease was determined by a gross estimation of the most severe reduction in cross-sectional area within a coronary artery or major branch thereof. We subdivided coronary disease into mild (50%-74% stenosis), moderate (75%-90% stenosis), and severe (>90% stenosis). Coronary artery disease in the cardiac allograft can be divided into 2 types: the focal eccentric atherosclerotic plaques seen in the general population (hereafter referred to as atherosclerosis) and the diffuse concentric fibrointimal thickening (hereafter referred to as fibrointimal hyperplasia) that is characteristic of transplanted hearts and is thought to represent chronic rejection.9-11 Although these 2 disease processes are not mutually exclusive,10 we assigned each patient to 1 category based on the predominant disease process present.

**Results**

**Patient Population**

The 39 autopsied patients were 29 men and 10 women; 26 were white, 12 were black, and 1 was Native American. Six pediatric patients ranged in age at transplantation from 18 days to 15 years (mean, 9.2 years). Pediatric survival ranged from 0 days to 3.2 years (mean, 339 days). The adults’ age range at transplantation was 30 to 61 years (mean, 48.1 years). Adult survival ranged from 0 days to 9.8 years (mean, 2.6 years). The indications for transplantation in adult, pediatric, and all patients are summarized in Table 1. These numbers are similar to those reported elsewhere.1,3,5,6

**Sudden Cardiac Arrest**

A subgroup of 7 patients who were in medically stable condition died after a sudden cardiac arrest (Table 2). Two deaths were attributed to graft vascular disease (GVD). Both patients had severe coronary artery fibrointimal hyperplasia. They lived 3.2 and 6.3 years, and both had evidence of myocardial ischemia in the form of an acute myocardial infarction or extensive, wavy fiber change. Two other deaths were attributed solely to cardiac arrhythmias only after no other clinical or anatomic cause could be found to explain the death; complete autopsies were performed on both. They had mild atherosclerosis. All of the aforementioned 4 patients had cardiac hypertrophy and/or dilation, which is an independent risk factor for arrhythmia and sudden death.12,13 Another patient died due to an arrhythmia during an exacerbation of acute renal failure. The last 2 deaths were due to acute cellular allograft rejection.

Two other patients died suddenly, but whether this was due to sudden cardiac arrest is unclear. One had a complex medical history that included Staphylococcus epidermidis sepsis and acute and chronic cerebrovascular accidents. Autopsy revealed mild coronary artery atherosclerosis and right and left ventricular hypertrophy (heart weight, 624 g). The second patient had a history of medical noncompliance and drug abuse and was admitted after 3 days of dyspnea and chest pain. Her initial admission drug screen was positive for cocaine, but a repeated screen was negative. She died suddenly soon after admission. Her cardiac pathology included mild coronary artery atherosclerosis and focal acute contraction band necrosis that was thought to be consistent with either the toxic effects of cocaine or aggressive resuscitation.

**Cause of Death**

The cause of death varied with increasing time from transplantation (Table 3). Right-sided heart failure, multisytem organ failure (MSOF), and preservation procurement injury are included in Table 3 as complications of transplantation because these deaths occurred during the immediate postoperative period and were related directly to transplantation.

**Early Deaths After Transplantation**

Fourteen patients died perioperatively or postoperatively without ever reaching a medically stable condition (Table 4). Thirteen died during the first month after transplantation, while 1 survived for 50 days. The causes of death in these
patients were as follows: right-sided heart failure, 6 (43%); MSOF, 4 (29%); preservation procurement injury, 3 (21%); and infection, 1 (7%).

The 6 patients who died of right-sided heart failure had clinically evident right ventricular failure immediately after transplantation. Four had elevated pulmonary artery pressures, while 2 had intractable right ventricular dysfunction. Autopsy revealed that all had acute myocyte necrosis that usually was most severe in the right ventricle. Four exhibited right ventricular dilation. In 5 of the 6 patients who died of right-sided heart failure, the lungs were examined at necropsy, and 4 had pathologic evidence of pulmonary hypertension. They had grade II to III pulmonary hypertensive arteriopathy based on the grading scheme of Heath and Edwards (grades I-VI).14

Two patients died on the day of transplantation due to preservation procurement injury. They could not be weaned off cardiopulmonary bypass owing to biventricular failure.

Their hearts had extensive acute necrosis of the right and left ventricles. The necrosis was associated with an early infiltration of neutrophils in one patient; the other patient did not have a notable inflammatory cell infiltrate. The third patient who died of preservation procurement injury had a transplant complicated by severe left ventricular dysfunction. He died 9 days after transplant, and the autopsy revealed patchy left ventricular organizing necrosis characterized by myocyte hyperesinophilia, a polymorphous inflammatory infiltrate, myophagocytosis, and interstitial hemorrhage.

Infections

Infections were the cause of death in 5 patients. Two patients died of acute bacterial pneumonia. The first died 15 days after transplantation, and cultures were positive for Escherichia coli and Enterobacter cloacae. The second died 35 days after transplantation; the organisms involved were Pseudomonas aeruginosa, gram-positive cocci, and

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Case No. & Survival After Transplant & Type of Coronary Artery Disease/Maximum Percentage Stenosis & Cardiac Pathology* & Comments & Cause of Death \\
\hline
1 & 41 d & Atherosclerosis/50-74 & RV and LV hypertrophy (522 g); RV dilation & Plasmapheresis & Arrhythmia \\
2 & 2.7 y & Fibrointimal hyperplasia/90 & Small healed or organizing LV infarcts & K+ = 7.5 mEq/L (7.5 mmol/L) & Exacerbation, acute renal failure \\
3 & 3.2 y & Fibrointimal hyperplasia/90 & RV and LV dilation; extensive wavy fiber change & — & GVD \\
4 & 6.3 y & Fibrointimal hyperplasia/90 & LV hypertrophy (559 g); RV dilation; & Hemodialysis & GVD \\
5 & 7.2 y & Atherosclerosis/50-74 & RV and LV hypertrophy (927 g); RV and LV dilation & Hemodialysis & Arrhythmia \\
6 & 1.9 y & Fibrointimal hyperplasia/50-74 & RV dilation; acute rejection (grade 3B) & — & Acute rejection \\
7 & 3.1 y & Atherosclerosis/50-74 & Acute rejection (grade 3B) & — & Acute rejection \\
\hline
\end{tabular}

GVD, graft vascular disease; LV, left ventricular; MI, myocardial infarction; RV, right ventricular.

* Only substantial ventricular hypertrophy and microscopic pathology are listed. The weights for hypertrophied hearts are listed parenthetically.
gram-positive filamentous organisms consistent with *Nocardia* species. One patient who survived 150 days after transplantation became critically ill after developing cytomegalovirus (CMV) colitis. The autopsy revealed CMV pneumonia and gastroenteritis with a concomitant infection of the lungs, brain, and skin by *Scedosporium apiospermum*. Another patient died 1.1 years after transplantation, after a lung infection due to *Aspergillus* species. The final patient died following CMV gastroenteritis that occurred 5.0 years after transplantation. His course was complicated by a central nervous system infection with human herpesvirus 6.

### Complications of Noncardiac Surgery

Three patients died of complications of noncardiac surgery. The first died 3.2 years after transplantation when an anal papilloma excision was complicated by sepsis due to *Pseudomonas* and *Candida* organisms. One month after a radical prostatectomy for prostate cancer, the second patient experienced wound dehiscence complicated by necrotizing fasciitis and peritonitis. He died 4.0 years after transplantation. The last patient underwent a right-sided upper lobectomy for squamous cell carcinoma of the lung, which was complicated by a polymicrobial pneumonia and sepsis due to *P aeruginosa* and *Candida albicans*. He died 9.8 years after transplantation.

### Acute Rejection

Acute cellular rejection is characterized by an inflammatory infiltrate that may be associated with damage to the heart. The International Society for Heart and Lung Transplantation assigns grades of 0 to 4, depending on the nature of the infiltrate and the presence of myocardial and vascular damage. Acute rejection was the cause of death in 3 patients. Two of them, aged 17 and 46 years, had sudden cardiac arrests and died 1.9 and 3.1 years after transplantation, respectively (cases 6 and 7, Table 2). Both had grade 3B rejection at postmortem examination. The third patient was a 46-year-old man who sought care 2 years after transplantation because of malaise, shortness of breath, and chest pressure. During evaluation, he had a cardiac arrest. The autopsy revealed grade 3B rejection in the heart.

### Malignant Neoplasms

Malignant neoplasms were the clear cause of death in 2 patients and the presumed cause in another. One patient was a 62-year-old man in whom fever, chills, and a pleural effusion developed 2.4 years after transplantation. When he died, Kaposi sarcoma involved his lung, liver, and skin. A second patient was a 43-year-old man in whom ascites, fever, shortness of breath, and renal failure developed 7.1 years after transplantation. He was diagnosed with diffuse large B-cell lymphoma. MSOF quickly developed, and when he died, lymphoma involved his mediastinal and abdominal lymph nodes, colon, omentum, pleura, small intestinal serosa, and splenic capsule. The third patient was a 49-year-old man who was being evaluated for pheochromocytoma. He had abdominal pain and hypertension 2.9 years after transplantation and then died after a cardiac arrest. The autopsy revealed an enlarged, mostly necrotic adrenal with medullary expansion, which was suggestive of pheochromocytoma. He had abdominal pain and hypertension 2.9 years after transplantation and then died after a cardiac arrest. The autopsy revealed an enlarged, mostly necrotic adrenal with medullary expansion, which was suggestive of pheochromocytoma. The postmortem heart exhibited rare foci of acute and chronic inflammation, as well as diffuse contraction band necrosis and wavy fiber change in all coronary territories of the left ventricle. These changes are consistent with catecholamine toxicity, as might be expected with a pheochromocytoma.

Seven additional patients had posttransplant malignant neoplasms; these often were multiple (Table 5). Skin cancers were common and found in 3 patients. A case of colon
Table 5
Malignant Neoplasms Occurring After Transplantation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Malignant Neoplasm</th>
<th>Transplant-Diagnosis Interval</th>
<th>Unexpected Neoplasm Found at Autopsy</th>
<th>Cause of Death</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Colonic adenocarcinoma</td>
<td>15 d</td>
<td>Yes</td>
<td>Unclear</td>
<td>15 d</td>
</tr>
<tr>
<td>2</td>
<td>Recurrent DFSP</td>
<td>1.1 y</td>
<td>No</td>
<td>Pulmonary embolus</td>
<td>1.8 y</td>
</tr>
<tr>
<td>3</td>
<td>Kaposi sarcoma</td>
<td>2.4 y</td>
<td>No</td>
<td>Kaposi sarcoma</td>
<td>2.4 y</td>
</tr>
<tr>
<td>4</td>
<td>Pheochromocytoma</td>
<td>2.9 y</td>
<td>No</td>
<td>Pheochromocytoma</td>
<td>2.9 y</td>
</tr>
<tr>
<td>5</td>
<td>Prostate carcinoma</td>
<td>3.6 y</td>
<td>No</td>
<td>Complications of noncardiac surgery</td>
<td>4.0 y</td>
</tr>
<tr>
<td>6</td>
<td>Skin, SCC</td>
<td>1.8 y</td>
<td>No</td>
<td>Infection (GI CMV)</td>
<td>5.0 y</td>
</tr>
<tr>
<td>7</td>
<td>Skin, SCC</td>
<td>1.8 y</td>
<td>No</td>
<td>DLBL</td>
<td>7.1 y</td>
</tr>
<tr>
<td>8</td>
<td>Lung, SCC</td>
<td>5.4 y</td>
<td>No</td>
<td>Unclear</td>
<td>7.2 y</td>
</tr>
<tr>
<td>9</td>
<td>Renal cell carcinoma, bilateral</td>
<td>9.6 y</td>
<td>Yes</td>
<td>Cirrhosis</td>
<td>9.6 y</td>
</tr>
<tr>
<td>10</td>
<td>Skin, SCC (2 occurrences)</td>
<td>7.6 y</td>
<td>No</td>
<td>Complications of noncardiac surgery</td>
<td>9.8 y</td>
</tr>
</tbody>
</table>

BCC, basal cell carcinoma; CMV, cytomegalovirus; DFSP, dermatofibrosarcoma protuberans; DLBL, diffuse large B-cell lymphoma; GI, gastrointestinal; PTLD, posttransplant lymphoproliferative disorder; SCC, squamous cell carcinoma.

cancer in a patient who died 15 days after transplantation was clearly incidental to the transplantation history. A patient who died of a pulmonary embolus had a recurrence of dermatofibrosarcoma protuberans (DFSP) that was diagnosed 26 years before cardiac transplantation. Two patients died of complications following surgical resection of their tumors: one had prostate adenocarcinoma and the other had squamous cell carcinoma of the lung. A patient in whom posttransplant lymphoproliferative disorder developed 4.6 years after transplantation later died of complications following a gastrointestinal CMV infection. An unexpected nodular sclerosis type Hodgkin lymphoma involving mediastinal lymph nodes was discovered at autopsy in a patient who had a sudden cardiac arrest (case 5, Table 2). This same patient had a lung squamous cell carcinoma resected 5.4 years after transplantation. Renal adenomas and carcinomas were a necropsy finding in 5 patients and were found in 17% (5/29) of autopsies that included examination of the abdomen.

Graft Vascular Disease

GVD was the cause of death in 3 patients. All had severe fibrointimal hyperplasia. One was a girl who was 13 years old at the time of transplantation and who survived 3.2 years before dying of a sudden cardiac arrest (case 3, Table 2). Her heart had diffuse, wavy fiber change and slight interstitial and perivascular fibrosis. A 51-year-old man who died 1.8 years after transplantation also died of a sudden cardiac arrest (case 4, Table 2). Multiple small acute infarcts were seen in the posterior and anteroseptal portions of the left ventricle; diffuse interstitial and perivascular fibrosis also were present. The last patient to die of GVD was a man who was 55 years old at the time of transplantation. He died 3.3 years after transplantation; he sought care because of 3 days of dyspnea and a syncopal episode. The autopsy revealed multiple acute, organizing, and old infarcts in the left ventricle.

Other Causes of Death

The causes of death in 4 patients are listed as other (Table 3). A 51-year-old man died 1.8 years after transplantation as a result of complications of a pulmonary embolus. A 53-year-old man with a medical history of hepatitis B and cirrhosis was admitted to the hospital 9.6 years after transplantation because of hepatic failure. Hepatitis B infection in heart transplant recipients is associated with active viral replication and an aggressive clinical course.17 He died due to hepatic encephalopathy and renal failure. A 61-year-old man had a massive hemorrhagic infarct in the left middle cerebral artery territory 2.7 years after transplantation. The fourth patient had a sudden cardiac arrest secondary to hyperkalemia and acute renal failure (case 2, Table 2).

Discussion

The causes of death in this study were complications of transplantation (13 [33%]), infection (5 [13%]), complications of noncardiac surgery (3 [8%]), acute rejection (3 [8%]), malignant neoplasm (3 [8%]), GVD (3 [8%]), cardiac arrhythmia (2 [5%]), other (4 [10%]), and unclear (3 [8%]).
Previous autopsy studies have found the causes of death to be infection (23%-34%), chronic rejection (20%-30%), acute rejection (14%-19%), graft coronary disease (7%-18%), malignant neoplasm (2.5%-10%), and operative complications of transplantation (4%-19%).\(^1\)\(^2\)\(^3\)\(^5\)\(^6\) Several factors may explain our higher rate of death due to complications of transplantation. The autopsy rate for patients dying within 1 month of transplant was 62% (13/21), while the overall rate for our study was 40% (39/97). Clearly, there was a bias toward obtaining autopsies of patients who died soon after transplantation. Our final analysis on the causes of death will, therefore, be skewed toward complications of transplantation. Also, we included deaths due to MSOF as a complication of transplant; similar deaths elsewhere may have been attributed to a terminal infection. Another factor that decreased the deaths attributed to infection was that we isolated a group of patients who died shortly after noncardiac surgery. Other studies may have classified these deaths as due to infection. Only 1 other study identified a cause of death as “complications to surgery, etc.” but no further description of this group was given.\(^5\) Previous studies that identified deaths due to chronic rejection used the criteria of coro

nary fibrointimal hyperplasia, interstitial fibrosis, and diffuse or nodular mononuclear aggregates of inflammation in an interstitial, perivascular, or vascular location.\(^5\)\(^6\) The deaths that we attributed to GVD could be considered by others as due to chronic rejection.

The causes of death in the 6 pediatric patients were right-sided heart failure (2 [33%]), preservation procurement injury (1 [17%]), acute rejection (1 [17%]), GVD (1 [17%]), and unclear (1 [17%]). Although interpretation of our data was hampered by the small sample, our results were not remarkably different from those of another study in which the reported causes of death were as follows: infection, 28%; rejection, 24%; graft coronary disease, 17%; pulmonary hypertension, 14%; nonspecific graft failure, 7%; and other, 10%.\(^2\) The 2 infants in our study died within 9 days of transplantation, consistent with the poor infant survival reported elsewhere.\(^1\) Two teenaged patients died of sudden cardiac arrest due to GVD and acute rejection (cases 3 and 6, Table 2). In the present study, these cases demonstrated the longest pediatric posttransplantation survival periods of 1.9 and 3.2 years, and both had evidence of coronary artery fibrointimal hyperplasia. GVD has been documented in children as young as 0.2 year after transplantation and has been associated with sudden death.\(^18\)

Thirteen deaths occurred during the first month after transplantation due to right-sided heart failure (6 [46%]), MSOF (3 [23%]), preservation procurement injury (3 [23%]), and infection (1 [8%]). Other studies have determined that early deaths were due to infection (29%-49%), graft failure (10%-52%), rejection (5%-22%), and pulmonary hypertension (15%).\(^3\)\(^6\)\(^19\) Similar results were reported in International Society for Heart and Lung Transplantation data.\(^1\) Once again, it is probable that we have sorted deaths differently from other studies.

More than half of our patients who died perioperatively or postoperatively without ever becoming medically stable had evidence of pulmonary hypertensive arteriopathy if their lungs were examined at autopsy. Eighty percent (4/5) of patients who died of right-sided heart failure had these changes if their lungs were evaluated. All had grade I to III lesions, and these are thought to be a reversible source of pulmonary hypertension.\(^20\)\(^22\) Only 2 patients who survived the perioperative period had pulmonary hypertensive arteriopathy. We suggest that even low-grade recipient pulmonary hypertensive arteriopathy is a risk factor for perioperative or postoperative death, particularly death due to right-sided heart failure. Increased preoperative pulmonary vascular resistance, even mild, has been reported elsewhere as an independent predictor of early mortality after transplantation.\(^3\)\(^23\)

Four patients died of MSOF with complicated clinical courses not easily attributed to a single underlying clinical or pathologic event. In all cases, however, transplant operations were complicated by right ventricular dysfunction or hypotension. It is possible that generalized ischemia from the transplant procedure led to injury to multiple organs, which culminated in MSOF and death. Although infections developed in 3 of the patients, the decline in their clinical condition preceded evidence of infection. Thus, infection was thought to be a result of MSOF and not the primary cause of death. Interestingly, 50% (2/4) of the patients with MSOF had pulmonary hypertensive arteriopathy that may have contributed to cardiac dysfunction after transplantation.

Right-sided heart failure was the main cause of perioperative and postoperative mortality during the first 9 years of the heart transplant program at DUMC (Table 4). Subsequently, MSOF became the leading cause of these deaths. This change suggests that better patient selection to exclude those with pulmonary hypertension or improved postoperative care occurred after those early years. Perhaps some of the patients who died of MSOF had cardiac dysfunction similar to that in patients who died earlier of right-sided heart failure; improved clinical management may have kept them alive long enough to develop MSOF.

Deaths 1 month to 2 years after transplantation accounted for 9 patients and were due to infection (3 [33%]), acute rejection (2 [22%]), MSOF (1 [11%]), cardiac arrhythmia (1 [11%]), unclear cause (1 [11%]), and other cause (1 [11%]). These results are similar to those reported elsewhere for deaths up to 1 year after transplantation.\(^1\)\(^6\)\(^19\)

Seventeen patients died more than 2 years after transplantation due to complications of noncardiac surgery (3
The lesions called adenomas varied from 0.2 to 1.2 cm in size and histologic features of these tumors, as well as the lack of metastatic disease, are similar in sclerotic or end-stage kidneys. Given the commonality at autopsy, but it is clear that they are more common in renal neoplasms of uncertain malignant potential. The relationship of acute cellular rejection to the development of coronary disease as reported in the literature is controversial; some studies have found a relationship between the two, while others have not.

Seven patients (18%) who were in medically stable condition died of sudden cardiac arrests, all more than 1 month after transplantation. They accounted for 27% (7/26) of the deaths after 1 month. Sudden cardiac death has been reported to occur in 10% of cardiac transplant recipients, with coronary artery disease being found in most of them.

Our data followed these trends. Both patients with fatal CMV infections died within 3 months of a grade 3A rejection episode. The fatal Aspergillus infection did not seem related to recent rejection. It seems likely that increased immunosuppression following clinically significant rejection predisposed to lethal opportunistic infection. In fact, 5% to 10% of infections beyond 6 months after transplantation are opportunistic and due to increased immunosupression secondary to recurrent or chronic rejection.

Although malignant neoplasms were documented in 10 patients (26%), only 3 (8%) died because of them. If we exclude the colonic carcinoma that was clearly incidental to transplantation, renal neoplasms, and the DFSP that occurred and recurred before transplantation, the incidence of malignant neoplasm drops to 18% (7/39), which is higher than the incidence of 3% to 16% reported elsewhere. The rate of malignant neoplasm, however, is dependent on the length of follow-up after transplantation. The most common malignant neoplasms after transplantation were skin cancers; 3 patients were diagnosed with a total of 6 squamous cell carcinomas and 1 basal cell carcinoma. An increased incidence of skin cancer, with a predominance of squamous cell carcinoma, has been well documented in heart allograft recipients. Lymphoma developed in 8% (3/39) of the patients; non-Hodgkin lymphoma and Hodgkin lymphoma accounted for 2 and 1 of these cases, respectively. Lymphomas are reported as the most common noncutaneous malignant neoplasms, with an incidence of 2% to 16% for non-Hodgkin lymphoma and 0.4% for Hodgkin lymphoma.

Colonc and prostate carcinoma were found in 1 patient each, while squamous cell carcinomas of the lung were found in 2. Although these carcinomas are reported by Penn as having no increased incidence in the transplant population, more recent data suggest that the incidence of lung and prostate carcinoma increases linearly more than 1 year after transplantation.

The time to development of the malignant neoplasm was quite variable. If we exclude the colonic carcinoma, DFSP, and renal neoplasms, the first malignant neoplasm seen was Kaposi sarcoma at 2.4 years after transplantation. Kaposi sarcoma generally is the first tumor seen and appears on average at 19 to 22 months after transplantation. Lymphomas were diagnosed 4.6 to 7.2 years after transplantation. Although 2 of the lymphomas occurred after the average of 32 to 56 months, both fell well within the published range of 0.5 to 254 months.

GVD was the cause of death in 3 patients. All had severe fibrointimal hyperplasia and evidence of acute and/or old ischemic injury to the heart. Two had interstitial and perivascular fibrosis. Such fibrosis may be the result of ischemic injury at the time of transplantation or previous bouts of rejection. Both of these patients had a history of 3 or more episodes of grade 3 rejection revealed by endomyocardial biopsy. The last patient had 1 previous episode of grade 3A rejection. None of the aforementioned patients had evidence of more than grade 1A rejection at autopsy or on their most recent endomyocardial biopsy. Thus, all 3 of the patients had at least 1 episode of grade 3 acute rejection revealed by a previous biopsy. The relationship of acute cellular rejection to the development of coronary disease as reported in the literature is controversial; some studies have found a relationship between the two, while others have not.

Infections after transplantation follow a well-established pattern: the usual postsurgical infections and pneumonia are seen during the first month; opportunistic infections predominate from 1 to 6 months; normal community-acquired infections, some opportunistic infections such as CMV colitis and retinitis, and viral driven malignant neoplasms (eg, postransplant lymphoproliferative disorder) are most common subsequently.

Five patients had renal adenomas or carcinomas found incidentally at autopsy. All arose in the setting of nephrosclerosis, and all were papillary neoplasms of low nuclear grade. The lesions called adenomas varied from 0.2 to 1.2 cm in diameter. The carcinomas were up to 1.5 cm. It is debatable how to classify small renal epithelial neoplasms found incidentally at autopsy, but it is clear that they are more common in sclerotic or end-stage kidneys. Given the similar size and histologic features of these tumors, as well as the lack of metastatic disease, it is probably best to consider them renal neoplasms of uncertain malignant potential.

Although malignant neoplasms were documented in 10 patients (26%), only 3 (8%) died because of them. If we exclude the colonic carcinoma that was clearly incidental to transplantation, renal neoplasms, and the DFSP that occurred and recurred before transplantation, the incidence of malignant neoplasm drops to 18% (7/39), which is higher than the incidence of 3% to 16% reported elsewhere. The rate of malignant neoplasm, however, is dependent on the length of follow-up after transplantation.
a patient who died suddenly and unexpectedly. Sudden cardiac death has been attributed to acute rejection and myocardial infarction. The fatal arrhythmia commonly was bradycardia or atrial tachyarrhythmia. The conduction system may be damaged by acute rejection, leading to arrhythmias and sudden death. Of the 5 patients who died of a sudden cardiac arrest not due to acute rejection, 3 (60%) had a history of 3 or more episodes of grade 3 rejection. In contrast, of the remaining 23 patients with complete biopsy rejection histories at DUMC, only 5 (22%) had this amount of rejection. No grade 4 rejection episodes were recorded for any of the patients. Three of the above 5 patients were undergoing hemodialysis or plasmapheresis. Another patient who died suddenly during hemodialysis had a complex medical history, mild coronary atherosclerosis, and 3 past episodes of grade 3 rejection. Although her cause of death was unclear, it is possible that she died of a fatal arrhythmia. We speculate that repeated episodes of grade 3 rejection may have damaged the conduction system. These hearts then were at increased risk of developing arrhythmias during the hemodynamic stresses of hemodialysis or plasmapheresis.

Acute rejection accounted for 2 deaths due to sudden cardiac arrest. The patients were 17 and 46 years old, and both had a history of depression. We suggest factors that increased the risk of noncompliance with the antirejection medication regimen, such as depression, pose a significant risk factor for death due to acute rejection.

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References


