Clinicopathological Conference

Cardiac Transplantation and Aspergillosis†

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Case Presentation

Toni L. Bransford, MD

A 31-year-old female heart transplant recipient was admitted to the hospital for a recent history of progressively worsening headaches. Her past medical history included doxorubicin (Adriamycin)-induced cardiomyopathy and cisplatin-induced nephropathy secondary to a nonrecurrent osteosarcoma that occurred in 1982; in 1991, she underwent orthotopic heart transplantation. After transplantation (at age 29), she was admitted on several occasions for organ rejection and for onset of moderate-to-severe headaches after an uneventful pregnancy. In September 1992, a complete neurological evaluation for the headaches was unrevealing, and she was treated symptomatically.

The patient was admitted to another hospital for worsening headaches in January 1993; her WBC count was 0, and a lumbar puncture indicated a pressure of 450 mm H2O. She was diagnosed with pseudotumor cerebri and given acetazolamide (Diamox). While hospitalized, she developed a low-grade fever, and empirical antibiotic therapy was begun with defervescence. She was subsequently transferred to the intensive care unit for acute worsening of liver and renal function with hepatic encephalopathy. Cyclosporine and azathioprine were discontinued, and prednisone was converted to solumedrol. Her neurological condition worsened with coma and seizures. Computed tomography (CT) scans of the brain were normal. Because of hepatic failure, she was transferred to another hospital for a possible liver transplant. A new CT scan of the brain (3 days after the previous scan) showed multiple, circumferential, low-density lesions. The lesions were considered representative of a possible infectious process, perhaps Nocardia, tuberculosis, septic emboli, toxoplasmosis, or fungus. Shortly thereafter, the patient’s pupils became fixed and dilated, she was declared brain dead, and she died within 24 hours. Autopsy findings included multiple hemorrhagic lesions with cerebral edema, moderate biventricular hypertrophy, and mild-to-moderate coronary atherosclerosis.

Diagnostic Imaging for Fungal Infections of the Central Nervous System

Clark L. Carrol, MD

The radiographic manifestations of fungal infections of the central nervous system are generally nondiagnostic. Aspergillus, however, has a predilection for infecting the immunocompromised host. When Aspergillus infection spreads to the brain by a hematogenous route, usually of pulmonary origin, the hyphae attack cerebral vessels, causing vascular occlusion. Alternatively, they may transgress vascular walls, resulting in a hemorrhagic infarction. This process may evolve into a septic infarction with associated cerebritis and abscess formation. Vascular distributions of the anterior and middle cerebral arteries are the most common regions of involvement. Granulomatous inflammation is uncommon. Initial findings from magnetic resonance imaging (MRI) show prolongation of both T1 and T2 relaxation with often-equivocal mass effect and minimal contrast enhancement. CT findings are virtually identical except that the lesions appear to have a lower density than the surrounding brain parenchyma (Fig 1). Ringlike abscess enhancement may eventually be observed. MRI should be considered the diagnostic imaging method of choice; its relative insensitivity to skull base artifact enables a more sensitive study of the entire brain, including the middle and posterior cranial fossae.1-3

Cardiac Toxicity of Doxorubicin

Robert S. Benjamin, MD; Michael S. Ewer, MD, MPH

The patient died of complications of a cardiac transplantation performed to control progressive congestive heart failure secondary to doxorubicin-induced cardiomyopathy. She had received a cumulative dose of 900 mg/m² doxorubicin by 24-hour continuous infusion during the curative treatment of her osteosarcoma. Cardiotoxicity is a potentially life-threatening complication of doxorubicin therapy; Gottlieb et al4 showed that the degree of cardiac damage was related to the cumulative dose. They proposed a cutoff cumulative dose of 600 mg/m² using a standard schedule, which was subsequently decreased to 550 mg/m² and 450 mg/m² and should probably be revised to 400 mg/m².

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Fig 1. Contrast-enhanced axial image of the brain at the level of the basal ganglia demonstrates multiple, low-density, nonenhancing lesions (arrows) scattered throughout gray and white matter. The largest of these lies in the right frontal lobe and creates a mild mass effect with consequent mild right-to-left subfalcine shift. None of these lesions were evident on a computed tomography scan obtained 3 days earlier.

There is considerable variability in the maximum cumulative dose of doxorubicin tolerated by individual patients; more recent studies have suggested guidelines based on cardiac structure, function, and clinical evaluation of the patient to help decide whether to continue or to stop doxorubicin. Our studies, which use a modified grading scale proposed by Mackay et al, have indicated that a high-grade endomyocardial biopsy (>1.5) is the best predictor of increased risk of developing heart failure should additional therapy with doxorubicin or a doxorubicin-containing regimen be continued.

Patients receiving doxorubicin are frequently monitored by multiple-gated image acquisition analysis or echocardiography to determine whether they can safely receive more of the drug. When the ejection fraction is abnormally low or has fallen by more than 15 percentage points, doxorubicin is frequently discontinued without regard to cumulative dose. This practice probably results in premature discontinuation of doxorubicin if the test is performed after a low cumulative dose. The most important way to predict whether a patient can safely continue doxorubicin or is at risk of developing potentially fatal cardiac toxicity is knowledge of the cumulative doxorubicin dose that has a minimal (<5%) risk of heart failure for the given dose schedule: 400 mg/m² by standard schedule, 650 mg/m² by 48-hour infusion, and 800 mg/m² by 96-hour infusion are conservative end points. At doses below these, only minimal cardiac monitoring is necessary. If these doses need to be exceeded for oncologic reasons or in cases where previous cardiac status suggests a significantly increased risk, complete monitoring, including endomyocardial biopsy, should be considered. Unfortunately, some patients will still develop heart failure, despite the most intensive monitoring program; in the treatment of a responsive malignancy, however, the risk of life-threatening cardiac failure is less than the risk of a suboptimal treatment curtailed by fear of potential cardiac dysfunction.

Transplantation and Rejection

Edward K. Massin, MD

Rejection of a transplanted heart occurs in various forms. Acute rejection, a cell-mediated reaction, is defined by the Transplant Research Cardiac Database as an event treated with increased immunosuppression. Acute rejection is generally diagnosed by an abnormal biopsy, and most episodes of acute rejection are asymptomatic. Ninety percent of such episodes occur within the first 6 months after transplantation. Episodes of acute rejection are rare after the first anniversary of transplantation, unless some change has occurred in the immunosuppressive regimen. Rejection accounts for approximately 17% of deaths. Acute rejection is more frequently associated with female recipients, young female donors, and HLA mismatch.

Noninvasive diagnosis of rejection is difficult, as techniques are relatively insensitive and specificity is poor. Biopsies are therefore done routinely, more frequently early after transplantation and with decreasing frequency as months and years pass. Rejection is graded by the extent of inflammatory infiltrate and myocardial destruction. With progressively severe rejection, perivascular inflammatory infiltrates spread to the interstitium, and myocyte destruction becomes an increasingly prominent feature.

Humoral rejection appears to be related to HLA-II antigens. Biopsy specimens will show deposits of immunoglobulin and complement on the vascular endothelium with endothelial swelling and activation. Humoral rejection is associated with increased fatality and may underlie the development of transplant coronary artery disease. Treatment is instituted for patients with hemodynamic compromise. Hyperacute early postoperative rejection is associated with HLA-I antigens. It may first be manifested by failure of spontaneous electrical activity to develop and by difficulty in pacemaker capture. An increased dose of inotropic agents may be necessary. The prognosis for a patient who has early postoperative humoral rejection is usually poor.

Allograft coronary artery disease is the leading cause of death after the first anniversary of transplantation. Its incidence is low during the first year after transplantation but reaches a range of 30% to 50% by 5 years. Thus far, the only successful treatment for transplant coronary disease is retransplantation. New approaches to the treatment of allograft coronary disease have been suggested and include monoclonal antibodies to interleukin-2 and to platelet-derived growth factor. Inhibitors of smooth muscle proliferation and migration, such
as low molecular weight heparin\textsuperscript{17} and angiopeptin,\textsuperscript{18} may prove to be of value.

**Immunosuppressive Therapy in Cardiac Transplantation**

**Branislav Radovančević, MD**

Immunosuppressive therapy can be roughly divided into three phases: an early, or induction, phase (just before and immediately after transplantation); a high-risk-of-rejection phase (during the first several months after transplantation); and a late, or long-term, maintenance phase. Presently, the therapy most frequently used in the induction phase is a triple-therapy protocol that consists of cyclosporine, steroids, and azathioprine. All patients receive 2 mg/kg azathioprine after surgery and 2 to 6 mg/kg cyclosporine on the basis of their renal function as assessed by serum creatinine and creatinine clearance. During surgery, 500 mg methylprednisolone is given before the release of the aortic cross-clamp. After surgery, methylprednisolone administration is continued and gradually tapered to 30 mg/d by day 11. Azathioprine is given at the dosage of 2 mg/kg per day and adjusted to achieve a WBC count in the range of 5000 to 7000. Cyclosporine is started at 6 mg/kg per day, and the dose is adjusted to maintain a serum level between 250 and 600 ng/mL, as measured by a whole blood monoclonal antibody (InCStar). In patients with perioperative renal or hepatic dysfunction, either orthoclone (OKT3) monoclonal antibody or ATGAM polyclonal antibody is used instead of cyclosporine to avoid resulting additional nephrotoxicity and hepatotoxicity.

Acute rejection episodes are rare by 6 months after transplantation, and the long-term maintenance phase of immunosuppressive therapy is begun at that time. A decrease in the dosage of cyclosporine from an average of 6.5 mg/kg per day at 6 months after transplantation to 3.8 mg/kg per day at 5 years significantly reduces the incidence of some side effects, such as seizures and lymphomas.\textsuperscript{19} This dose reduction also helps stabilize renal function, which worsens during the first 6 months after transplantation.\textsuperscript{19}

During the past several years, many new immunosuppressive drugs have been introduced into clinical trials. The new macrolide substitute for cyclosporine, FK506, has been proven in clinical trials to be a more potent immunosuppressant than cyclosporine but has not alleviated problems related to renal function\textsuperscript{20}; FK506 is also neurotoxic. The severity of these side effects, however, may be reduced by decreasing the dose. Another new drug, rapamycin, has a similar toxicity pattern but may be more effective because it is synergistic when used with cyclosporine, thereby enabling a large dose reduction of both cyclosporine and rapamycin.\textsuperscript{21}

**Infections in Cardiac Transplant Patients**

**Barry J. Zeluff, MD**

Infectious complications in cardiac transplant patients follow a pattern based on the level of immunosuppression and the time elapsed since transplantation. The first period occurs during the first 1 to 2 months after transplantation. Even though the initial levels of immunosuppressive therapy are high, the full immunosuppressive effect generally has not been reached, and the most common infections are those nosocomial infections that occur with other types of cardiovascular surgery: nosocomial bacteremias, wound infections, urinary tract infections, or pneumonia. Nosocomial pneumonias are more prevalent and generally more serious.

The second period occurs after 1 to 2 months of immunosuppressive therapy: opportunistic infections become the predominant problem. The period of greatest risk for opportunistic infections is generally within the first 6 months after transplantation, but it can extend to 12 months assuming an uncomplicated course of immunosuppressive therapy. Because cell-mediated immunity is affected more than humoral immunity, a characteristic group of pathogens commonly cause the opportunistic infections.

Viral infections are by far the most common, and among these, the members of the herpesviridae family predominate.\textsuperscript{22} Herpes simplex types 1 and 2 occur most often. Cytomegalovirus (CMV), however, is the major cause of morbidity and mortality in transplant patients.

Protozoan, bacterial, and fungal opportunistic infections are also prevalent in cardiac transplant patients. Currently, the most common protozoan infection is *Toxoplasma gondii*, which usually presents with cardiac or central nervous system manifestations. Among the opportunistic bacterial infections, Legionnaire's disease is the most common; it occurs in both the endemic and epidemic form in transplant patients. Higher bacteria such as *Nocardia* spp. are also common. They generally present initially with a pulmonary focus but can readily disseminate and are often difficult to eradicate. *Mycobacteria*, both tuberculous and nontuberculous, are also frequent infections in transplant patients. Among fungal infections, *Candida* spp., particularly *Candida albicans*, are the most prevalent.

After the first anniversary of a cardiac transplantation, the only opportunistic infections that tend to persist are granulomatous infections such as fungi or mycobacteria. The fungal infections associated with the greatest morbidity and mortality in cardiac transplant patients are those caused by *Aspergillus* spp. These are ubiquitous fungi that are common infections in transplant patients who are severely immunosuppressed or have had recent CMV infections. They generally present with a pulmonary focus but often disseminate and have a tendency to invade blood vessels and the central nervous system.\textsuperscript{23}

**Aspergillosis and Immunosuppression**

**L. Maximilian Buja, MD**

The pathological findings in this case correlate with the patient’s final clinical course. Chronic immunosuppressive therapy for a heart transplant was followed by the development of septicemia, encephalopathy, and hepatic failure. Although the immunosuppressive therapy was discontinued, the patient developed disseminated aspergillosis, a well-known, serious complication of immunosuppressive therapy, which according to one study occurs in 10.7% of immunosuppressed patients.\textsuperscript{24}

Disseminated invasive aspergillosis mainly occurs in severely immunocompromised patients, either from prolonged leukopenia secondary to cytotoxic chemotherapy or from immunosuppressive agents in organ recipients.\textsuperscript{25} Most cases of invasive aspergillosis presumably result from inhalation of conidia. The lungs are
usually the initial focus of infection. The pulmonary disease arises by germination of the conidia followed by endobronchial proliferation of hyphae into pulmonary arterioles and lung parenchyma and subsequent ischemic necrosis. In addition, Aspergillus hyphae have a propensity to invade blood vessels, resulting in hematogenous dissemination with thrombosis, hemorrhagic infarction, and invasion of distant organs. The brain is the most common site of spread beyond the lungs (Fig 2). Other sites of hepatogenous dissemination include the gastrointestinal tract, skin, heart, bone, liver, spleen, kidney, thyroid, diaphragm, bladder, peritoneum, ear, and muscle. The signs and symptoms of invasive aspergillosis are nonspecific. Diagnosis is often difficult, and despite the propensity for vascular invasion, positive blood cultures rarely occur.25

Aspergillosis of the central nervous system takes the form of brain abscesses. The patients present in one of two fashions: rapid development of a stroke-like syndrome or subacute deterioration in mental status with progressive obtundation, which probably occurred in this patient. If aspergillosis is diagnosed, treatment is often unsuccessful: mortality rates range from 40% to 69% in treated patients.26

Conclusion
Edward K. Massin, MD

This case demonstrates the promises, curses, and frustrations of managing complex medical problems in an era of high technology. Osteosarcoma, a life-threatening malignancy, was cured at the cost of this young woman's heart function. Even careful monitoring of the doxorubicin dose was not adequate to prevent cardiomyopathy. After heart transplantation, her clinical course was marked by recurrent episodes of rejection and finally by a fatal fungal infection. Clearly, in this age of sophisticated technology, we remain in need of more selective therapy for malignancies (to avoid cardiotoxicity and other harmful side effects), and we need more selective immunosuppressive drugs (to prevent rejection of the transplanted organ while maintaining resistance to infection).

A question not even addressed by this discussion is the development of successful treatment for end-stage congestive heart failure by means other than transplantation. Will we in the future have the capacity to interrupt the destructive processes that lead to cardiomyopathy and the ability to stop myocardial destruction and the development of fibrosis? Will we find a way to stimulate the embryonic capacity of the myocardial cell to proliferate? Will there become available the means to enhance the contractile properties of remaining myocytes? Will we overcome the limitations of the mechanical heart to provide circulatory support and, in doing so, create a whole new set of issues for future consideration?

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