THE FIRST PEDIATRIC JAPANESE CASE TO UNDERGO HEART TRANSPLANTATION IN THE UTAH CARDIAC TRANSPLANT PROGRAM IN THE UNITED STATES

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A seven-year-old girl underwent heart transplantation because of progressive congestive heart failure resulting from familial dilated cardiomyopathy. Her parents were second cousins to each other and her brother had died of dilated cardiomyopathy. Her symptoms of congestive heart failure began four months before the transplantation and became gradually worse. Left ventricular ejection fraction was 10 to 20% echocardiographically, and mitral and tricuspid valve regurgitation were present. Her condition of NYHA IV was not improved by treatment with dobutamine infusion and isosorbide dinitrate. She was transported to the Primary Children's Medical Center in Utah, USA, on July 22, 1991 in critical condition to undergo heart transplantation. Despite treatment with amrinone and additional catecholamines, she became semi-comatose due to ischemic liver injury on July 24, 1991. A donor became available on July 25, 1991, and the transplantation was performed. Cardiac ischemic time was 97 min. Although she had transient OKT3 monoclonal antibody-related encephalopathy on her fifth postoperative day, she recovered normally. She had moderate rejection on the 20th postoperative day and mild rejection on the 79th and 149th postoperative days. She has had no significant infectious diseases. The baseline examination performed three months after heart transplantation revealed no abnormal findings on her coronary arteriogram. She returned to Japan and has been attending elementary school. The annual examination of her transplanted heart showed neither stenosis nor occlusion in her coronary angiogram. She has been receiving cyclosporine, azathioprine, and a low dose of prednisone as an immunosuppressive regimen. If she does not exhibit rejection, the use of steroids will be decreased or discontinued.

(*Jpn Circ J* 1993; **57**: 873–882)

ACCORDING to the International Society of Heart Transplantation¹, 16,687 heart transplantations have been performed since the first heart transplantation by Dr. Chris-

Key words:

Dilated cardiomyopathy
Heart transplantation
UTAH cardiac transplant program

tian Barnard in 1967? The current one-year survival rate of 82% reflects advances in organ procurement and immunosuppression. The age range of recipients has been expanded to include infants, and the treatment of end-stage pediatric heart disease with heart transplantation has become routinely

(Received September 10, 1992; accepted March 18, 1993)

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Fig.1. A series of chest roentgenograms. Gradually increasing cardiac size can be observed.

available within the past several years. The thirtieth heart transplantation world-wide, and the first in Japan, was performed in 1968 by Dr. Juro Wada. Dr. Wada, of the Sapporo Medical College, tried to encourage heart transplantation in Japan. However, heart transplantation has not been performed in Japan since then, although some cardiac surgeons and cardiologists have been preparing to begin performing heart transplantation surgery.

We recently had the opportunity to study a seven-year-old Japanese girl who received a heart transplantation in the UTAH (Utah Transplantation Affiliated Hospitals) Cardiac Transplant Program in the United States because of severe congestive heart failure resulting from a familial dilated cardiomyopathy.

CASE REPORT

A 7-year-old girl was admitted to the

Kofu Municipal Hospital on April 15, 1991, with chief complaints of anorexia, shortness of breath and malaise, which had appeared in April, 1991. She showed severely dilated left and right ventricles and regurgitation of both mitral and tricuspid valves. She was treated with digitalis and diuretics, but her general condition became gradually worse. She was transferred to the Kofu National Hospital on June 26, 1991, in an attempt to control her congestive heart failure and to evaluate the possibility of becoming a candidate for pediatric heart transplantation. Her family history was significant because her second brother had developed dilated cardiomyopathy at age four and died suddenly on May 31, 1986, 8 months after his cardiac symptoms had appeared. Her eldest brother, father and mother showed no heart-related abnormalities. However, her parents were second cousins to each other.

The patient was born by full-term delivery. She had been healthy until April, 1991.

Fig.2. Electrocardiograms on April 15, 1991, and on June 26, 1991, when the patient was admitted to our hospital. On June 26, 1991, the voltage in the precordial leads was slightly less than that in the electrocardiogram on April 15, 1991.

Since her admission to the Kofu Municipal Hospital, she was treated with digitalis (digoxin: 0.23 to 0.25 mg/day) and furosemide (1 mg/kg/day) and her sodium intake was limited (3 to 4g/day). Her left ventricular function gradually deteriorated despite this therapy.

Pertinent physical findings at admission to our hospital included a height of 120.4 cm, body weight of 29.3 kg, blood pressure of 102/70 mmHg, pulse rate of 116/min, pale skin, dilatation of the jugular vein and enlarged cardiac dullness. Moist rale at the bases of both lungs, the third and fourth heart sounds, and a pansystolic regurgitant murmur at the apex (Levine II/VI) and at the fourth interspace of the left sternal border (Levine III/VI) were audible. In her abdomen, the liver was palpable 3 finger-breadths below the costal margin at the right mid-clavicular line. Peripheral edema was also present.

Laboratory findings were as follows. Her blood type was O and Rh-positive. A complete blood count showed a hemoglobin level of 15.0 g/dl, a red blood cell count of $556 \times 10^4/\text{mm}^3$, a hematocrit of 44.5%, a white blood cell count of $8500/\text{mm}^3$, and a platelet count of $34.5 \times 10^4/\text{mm}^3$. Erythrocyte sedimentation rate was 3 mm/h. Serum electrolytes included Na at 140 mEq/L and K at 4.1 mEq/L. The serum creatinine level was 0.83 mg/dl, the blood urea nitrogen level

was 15 mg/dl, and the uric acid level was 13.6 mg/dl. Liver function studies were as follows: serum total bilirubin, 1.92 mg/dl with direct bilirubin, 0.64 mg/dl; serum glutamic oxaloacetic transaminase, 40 IU/L; serum glutamic pyruvic transaminase, 54 IU/L; alkaline phosphatase, 553 IU/L; lactate dehydrogenase, 509 IU/L; and gamma-glutamyl transpeptidase, 49 IU/L. The serum creatinine phosphokinase level was 42 IU/L. Anti-HLA antibody (A, B, C-locus) was 0% in both positive rate and strength index. Tuberculin skin test was negative. Arterial blood gases obtained while the patient was breathing room air showed a pH of 7.518, an arterial carbon dioxide tension (PaCO_2) of 27.4 torr, and an oxygen tension (PaO_2) of 109.7 torr. The examination of viral antibodies revealed the following: Herpes simplex virus-IgG < 16, herpes simplex virus-IgM < 10, hepatitis A virus-IgM negative, hepatitis Bs antigen negative, hepatitis C antibody negative, HIV negative, EBV-IgM < 10, cytomegalovirus (CMV)-IgG 128, CMV-IgM < 10, toxoplasmosis-IgG < 16, and toxoplasmosis-IgM < 10.

A series of chest roentgenograms showed gradually increasing cardiac size, in spite of intensive therapies (Fig. 1).

Her electrocardiograms showed sinus tachycardia and atrial overload. On June 26, 1991, the voltage in the precordial leads was slightly less than that in the electrocardio-

A

B

C

Fig.3. M-mode (A), two-dimensional (B), and color-doppler (C) echocardiogram. They show a severely dilated left ventricle and left atrium, severe hypokinesis of the left ventricular wall, low cardiac output and pulmonary hypertension. The ejection fraction was 10%. Grade II to III mitral and tricuspid valvular regurgitation were observed.

Fig.4. The light (top) and electron (bottom) microscopic findings of the patient's native heart. The light microscopic findings revealed multifocal, irregularly distributed, myocardial fiber hypertrophy. Interstitial fibrosis was observed throughout, but no significant inflammatory change was observed. Electron microscopic findings revealed myofilament loss and the presence of irregularly sized mitochondria with prominent tubular cristae and granular matrices.

gram of April 15, 1991 (Fig. 2). Twenty-four-hour Holter electrocardiogram showed occasional unifocal ventricular premature beats of Lown's grade II.

Her echocardiograms showed severe hypokinesis of the left ventricular wall ($EF=10\%$). Left ventricle and left atrium were severely dilated ($LVDd=55$ mm, $LVDs=50$ mm). Grade II to III mitral and tricuspid regurgitation were found (Fig. 3). Left ventricular function did not improve despite intravenous dobutamine infusion (5 μ g/kg/min).

Her hemodynamic variables, as determined using a Swan-Ganz catheter, on July 2, 1991, were as follows: heart rate, 116 per min; cardiac index, 1.09 L/min/ M^2 ; mean

right atrial pressure, 18 mmHg; right ventricular pressure, 42/14 mmHg ($EDP=18$ mmHg); pulmonary arterial pressure, 42/26 mmHg; mean pulmonary arterial wedge pressure, 30 mmHg; and systemic blood pressure, 100/59 mmHg. These data were obtained free from the influence of an intravenous catecholamine.

She became unable to stand or walk around her bed, and her appetite was low. Her condition remained NYHA IV despite an increase of intravenous dobutamine and additional treatment with a low dose of isosorbide dinitrate.

She was transported from the Kofu National Hospital to the Primary Children's Medical Center in Utah, USA, on July 22, 1991, by a combination of ground ambulance, helicopter, and commercial jet airplane. The transfer took about 18 h. Although the patient showed no extraordinary signs at departure, whenever she was moved to a different vehicle, or when the aircraft landed, she showed unexpected sinus tachycardia, ventricular premature beats, and a drop in blood pressure at the midpoint of the transpacific flight where the aircraft altitude was 37,000 ft.

As soon as she arrived at the Primary Children's Medical Center, she was brought to the Intensive Care Unit and evaluated for heart transplantation. She was evaluated as a status I candidate.

Two days after her arrival, her laboratory findings showed a total bilirubin level of 2.8 mg/dl, a direct bilirubin level of 1.2 mg/dl and a serum glutamic pyruvic transaminase level of 660 IU/L. She became somnolent toward evening. The following day she became semicomatose with deteriorating liver dysfunction: total bilirubin, 4.7 mg/dl; direct bilirubin, 2.5 mg/dl; and serum glutamic pyruvic transaminase, 1927 IU/L. Her liver dysfunction was thought to be secondary to ischemic liver injury because she did not have abnormal findings suggestive of viral hepatitis. Although 10 μ g/kg/min of amrinone was administered, her hemodynamic findings showed no significant improvement.

A heart became available from a 6-year-old male, 25 kg, O-positive local donor at this time. This donor was CMV-negative. Although her pulmonary vascular resistance was 9.0 units at this time, this decreased to

Fig. 5. The light microscopic (hematoxylin and eosin stain) (left-top: lower magnification, left-bottom: higher magnification) and representative immunohistologic (right) findings of the biopsied specimen taken 20 days after the heart transplantation. The light microscopic findings revealed a fairly extensive interstitial and perivascular infiltration of mononuclear cells with associated myocyte degeneration, interstitial hemorrhage, and occasional interstitial neutrophils. There was also vascular prominence with endothelial cell swelling and an increase in the mural cellularity of small vessels. Immunohistologic findings demonstrated interstitial and vascular HLA-DR staining in addition to vascular accumulation of IgM, C3, C1q, as well as fibrin. The biopsied specimen taken after treatment with intravenous methylprednisolone (500 mg) for three days revealed no evidence of rejection.

4.5 units by treatment with 3 $\mu\text{g/kg/min}$ of nitroprusside. Her hemodynamics were acceptable for heart transplantation. Her heart transplantation was performed by a standard procedure toward evening on July 25, 1991. Total bypass time was 65 min and cardiac ischemic time was 97 min. The weight of the patient's native heart was 202g and both ventricles were quite dilated. The tricuspid and mitral valves were normal. Light microscopic findings revealed multifocal, irregularly distributed, myocardial fiber hypertrophy. Subendocardial scarring was observed throughout, but no significant inflammatory change was observed (Fig. 4,

top). Electron microscopic findings revealed myofilament loss and the presence of irregularly sized mitochondria with prominent tubular cristae and granular matrices (Fig. 4, bottom).

Immunosuppressive therapy using OKT3 monoclonal antibody as an early prophylactic regimen was begun in accordance with the protocol of the UTAH Cardiac Transplant Program (UCTP)³⁻⁶. Fifty milligrams of azathioprine was administered just before the surgery as an initial dose. During the operation, 5 mg of OKT3 monoclonal antibody was given intravenously after 250 mg of methylprednisolone. On the day after sur-

gery, she received 2.5 mg of OKT3 monoclonal antibody, 50 mg of azathioprine, 65 mg of methylprednisolone three times, and 65 mg of ganciclovir (DHPG) twice. Concomitant immunosuppression consisted of low-dose prednisone (0.25 mg/kg/day); azathioprine (approximately 2 mg/kg/day), titrated to a white blood cell count of 4000 to 6000/mm³; and cyclosporine, beginning on postoperative day four at 4 to 6 mg/kg/day and titrated to trough whole blood radioimmunoassay, using a monoclonal antibody level of 300 to 400 ng/ml.

She awoke the next day and showed a normal recovery. However, on her fifth postoperative day, she became somewhat encephalopathic, and exhibited disorientation, and a loss of responsiveness. An examination of her cerebrospinal fluid, blood and urine, a viral antibody examination and a brain CT scan also showed normal results. This neurological abnormality was thought to be OKT3 monoclonal antibody-related encephalopathy.⁷ OKT3 monoclonal antibody was discontinued and Minnesota Horse ALG was begun. She showed an impressive improvement over the next few days, and became neurologically appropriate. She left the Intensive Care Unit on her eighth postoperative day and was discharged from the Primary Children's Medical Center on her thirteenth postoperative day. At the time of discharge, the patient had significantly improved, and was alert and walking to some degree.

Routine posttransplantation examinations were performed according to the UTAH Cardiac Transplant Program protocol³⁻⁶. She showed moderate mixed rejection (C4 V3 by UCTP criteria⁸) (Fig. 5) on August 14, 1991, i.e. 20 days after her heart transplantation. This rejection was treated with intravenous methylprednisolone (500 mg) for three days, although she was asymptomatic. She showed mild rejection on the 79th and 149th postoperative days. Baseline examination of her transplanted heart was performed on November 12, 1991. Her coronary angiogram showed no abnormal findings such as diffuse stenosis or occlusion which would suggest chronic rejection. Other examinations revealed no abnormal findings.

She showed no infectious diseases and returned to Japan on February 15, 1992, six

and one-half months after her heart transplantation.

She has been attending elementary school since the beginning of the new semester in April, 1992, and has spent every day in regular classwork. The function of her transplanted heart has been noninvasively examined once a month by echocardiography. Her echocardiographic % fractional shortening has been within normal limits. An endomyocardial biopsy for monitoring rejection has been performed every 2 to 4 months. She has had neither episodes of rejection nor significant infectious disease since she returned to Japan. She has been receiving cyclosporine, azathioprine, and a low dose of prednisone as an immunosuppressive regimen. The blood level of cyclosporine, white blood cell count, other laboratory findings, and physical findings have been checked every 2 to 4 weeks. The annual examination of her transplanted heart revealed neither stenosis nor occlusion in her coronary angiogram.

DISCUSSION

During the past two decades, as heart transplantation has become an established modality in the treatment of end-stage heart disease, an increasing number of heart transplants have been reported in children. According to the Registry of the International Society for Heart Transplantation concerning pediatric heart transplantation,⁹ 909 transplantations have been performed in 874 patients between the ages of 0 and 18 years by 105 transplant centers. This number has been gradually increasing.

In Japan, the first heart transplantation was performed in 1968 by Dr. Juro Wada, of the Sapporo Medical School. However, the procedure has not been performed since then.

In recent years, more successful heart transplantations have been performed and a better survival rate has been reported in other countries. As a result, more patients with end-stage heart failure and more cardiac surgeons and cardiologists wish to begin performing heart transplantation again in Japan. Japanese patients with fatal, severe heart failure have had to leave Japan to receive heart transplantation. The case

presented here is the first Japanese pediatric case to receive a heart transplantation in the United States.

The heart transplantation in this case was performed with the patient in a critical condition: i.e., she was semicomatose due to ischemic liver injury.

Her posttransplant course has been uncomplicated except for transient OKT3 monoclonal antibody-related encephalopathy. OKT3 monoclonal antibody has been regarded as the most significant immunosuppressive agent to be introduced to organ transplantation since cyclosporine. It is well-known that the adverse effect profile of OKT3 monoclonal antibody includes high fever, chills, rigors, tremor, nausea and vomiting, and diarrhea. However, the incidence of encephalopathy associated with OKT3 monoclonal antibody administration is unknown. Premarketing data demonstrated that 16 of 977 patients (2%) required a lumbar puncture after OKT3 monoclonal antibody administration, with only seven providing complete information for evaluation. Six of the seven patients had negative bacterial, fungal, and viral cerebrospinal fluid cultures.⁷ This patient did not show abnormal values in the examination of cerebrospinal fluid, blood and urine, in the viral antibody examination, or in brain CT scans.

It is noteworthy that this patient has had only one episode of moderate rejection, two episodes of mild rejection, and no episodes of significant infection. Her baseline and annual examinations, which have included coronary arteriography, have revealed no abnormal findings and her echocardiographic % fractional shortening has been within normal limits. Although it has been reported that risk factors for chronic rejection, i.e., for allograft coronary artery disease, have included hypertriglyceridemia^{10,11} multiple episodes of rejection¹² increased donor age¹³ and the lack of anticoagulant/antiplatelet therapy,^{14,15} the pathogenic mechanisms responsible for the development of allograft coronary artery disease are thought to be immunologic. It has been reported that there is a significant relationship between allograft coronary artery disease and humoral immunity. Rose et al reported that patients with anti-HLA-antibodies had a decreased

five-year graft survival (50% vs 90%).¹⁶ Similarly, Hammond et al concluded that vascular deposition of immunoglobulin and complement on endomyocardial biopsy specimens which were taken within the first 30 days after surgery could be used to predict poor long-term graft survival.⁸ Recently, a strong correlation between allograft coronary artery disease and CMV infection has been reported.¹⁷⁻¹⁹ Normann et al reported that three of seven patients with vascular rejection (43%) were CMV-negative recipients of CMV-positive donors, a situation known to create a high risk of posttransplant CMV infection.¹⁹ As we mentioned previously, this patient's coronary arteriograms at 3 and 14 months after the heart transplantation showed no stenotic lesions. She originally had anti-CMV-antibody (IgG) and the donor was CMV-negative, which means that she was not at a high risk of CMV-infection. She also had no positive anti-HLA-antibodies and was cross-match negative. These findings, as well as only a few episodes of acute rejection, suggest that this patient is unlikely to develop allograft coronary artery disease. Due to the lack of evidence of subsequent episodes of rejection with vascular involvement, this patient is not likely to be a candidate for vascular rejection.⁸ Regarding the relationship between the type of rejection and the development of allograft coronary artery disease, Hammond et al reported that the risk of developing allograft coronary artery disease within five years was higher for patients with vascular rejection than for patients with cellular and mixed rejection.²⁰

The transplantation in the present case was gender mismatched: i.e., the donor was male while the recipient was female. According to a report by Esmore et al, females are likely to have rejection more frequently and sooner than males.²¹ They also reported that gender mismatching might predict the need for maintenance steroid more frequently in females.²¹ Although the present case had only three episodes of rejection, two of these episodes occurred just after steroid administration was discontinued. We now plan to taper the steroid dosage very slowly.

Fortunately, the present case has had no episodes of significant infectious disease. Infection still remains the most common cause

of morbidity and mortality after heart transplantation. Although the majority of infectious complications occur early, usually less than one year after heart transplantation, these patients should always be monitored for infection.

According to the reports concerning the quality of life after heart transplantation by Gaudiani et al²² and Lough et al²³, 86 to 89% of patients have a good or very good quality of life, which is altered by the adverse effects of immunosuppressive therapy. The present patient goes to school every day and is able to participate in gymnastics. She was able to go skiing six months after her heart transplantation and she is similar to other children from the standpoint of daily activity.

Heart transplantation in children has become accepted as an established treatment for end-stage heart disease. However, transplant patients must continue to receive immunosuppressive therapy for the rest of their lives. Naturally, they must overcome the adverse effects of immunosuppressants, i.e., renal impairment, hypertension and infection. Thus far, the present case has shown neither renal impairment nor hypertension. Growth retardation is the drug side-effect that most concerns clinicians who administer long-term steroid therapy to children aged 10 to 12 years or younger. The present case grew 4 cm in 10 months after steroid therapy began to be tapered and she appears to be growing normally. Another major concern with immunosuppressive therapy is the increased risk of tumor development. Although lymphoproliferative tumors have resolved upon reduction of cyclosporine, azathioprine, and steroids, this patient should be checked carefully for the rest of her life.

In conclusion, this case should serve as an important impetus for re-establishing heart transplantation in Japan and should highlight various aspects concerning heart transplantation.

Acknowledgment

We gratefully acknowledge Prof. Morie Sekiguchi, 1st Department of Internal Medicine, Shinshu University School of Medicine, for his critical reading of this case report.

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