Post Transplanted Infective Endocarditis

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The patient, a 51-year-old man, was receiving immunosuppressants for 2 yr after renal allotransplantation. He had heart failure with aortic regurgitation, fever, anemia and a history of odontectomy on admission. He was resistant to medical treatments and died from cerebral emboli. On autopsy, vegetation of the aortic valve was identified. Progression of atherosclerosis, which may have been due to steroids and chronic rejection, was prominent. This report is the first case of infective endocarditis following organ transplantation in Japan. Such complications as infective endocarditis and atherosclerosis will be on the rise with the increase of numbers of organ transplantations.

Key words: Infective endocarditis, Renal transplantation

Recently an improved survival rate after organ transplantation has been realized with the advent of various new immunosuppressants, but infectious diseases as complications due to the use of these agents are important problems and presently are the most common cause of death of organ recipients (1, 2). Among the various infectious complications, infection of respiratory, urinary and digestive tracts are frequent (3–5), while infective endocarditis is rarely reported. There are only a few published cases in Euro-US areas (6), and still no cases have been published yet in Japan (7, 8). Vascular accidents due to severe atherosclerosis are also reported as complications after organ transplantations (9). The use of immunosuppressive agents including steroids and chronic rejective reaction are presumed to be the cause of the rapid progression of atherosclerosis. The present report describes the first case in Japan of a transplant patient complicated with infective endocarditis with severe aortic regurgitation who showed severe atherosclerosis, as proven in the autopsy examination, 2 yr after renal allotransplantation.

CASE

A 51-year-old man with chronic renal failure received hemodialysis from 1982 and underwent renal transplantation at the Department of Urology of Hyogo College of Medicine Hospital on July 25, 1986. No hypertension or cardiac murmur was pointed out at that time. Later, 50 mg azathioprine, 8 mg methylprednisolone, and 150 mg mizoribine per day were administered orally as immunosuppressive agents. Two years later, he had nocturnal dyspnea and was diagnosed as congestive heart failure in May 1988. Although he transiently recovered with medical treatments, the symptoms of congestive heart failure recurred and he was admitted to our department for further examinations. The patient had a history of odontectomy 4 months before.

Physical examination demonstrated that pulsation of the internal jugular vein rose to 7 cm H₂O at 45 degrees of Fowler's position, and holosystolic murmur (Levine 4/6) of the apex coupled with a to-and-fro murmur (Levine 5/6) at the second
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Intracostal space at the left sternal border were audible. The blood pressure in the upper and lower limbs was 142/0 mmHg and 180/20 mmHg, respectively. His body temperature was 37.5°C.

The results of routine laboratory tests demonstrated normocytic and normochromic anemia (the red-blood-cell count was $319 \times 10^6$, the hemoglobin 8.4 g/dl) and the existence of inflammation (erythrocyte sedimentation rate was 22 mm/h, C-reactive protein $1^+$). The arterial gas analysis showed an oxygen tension of 63.4 mmHg indicating the presence of hypoxia (Table 1).

Although there was no remarkable abnormality in chest roentgenographic findings prior to hospitalization (on March 23, 1987), cardiomegaly with a cardio-thoracic ratio (CTR) of 65% and pulmonary congestion with bilateral pleural effusion were noted on admission. After hospitalization, the patient proved resistant to medical treatments, and an extended CTR and an increase in lung congestion were found in the chest roentgenogram on November 18 (Fig. 1).

An electrocardiogram obtained at the time of renal transplantation (July 25, 1986) revealed no significant abnormalities, but exhibited left ventricular hypertrophy at the time of admission (Fig. 2).

An echocardiographic examination showed a dilated left ventricle (diastolic dimension, 65 mm; systolic dimension, 55 mm) with mild hypertrophy (diastolic thickness, 12 mm). Although no definite vegetation showing a shaggy pattern in a M-mode echocardiogram was found in the aortic valve, the

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**Table 1. Laboratory findings at the time of admission.**

<table>
<thead>
<tr>
<th>Hematological tests</th>
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<tbody>
<tr>
<td>RBC $319 \times 10^6$/mm³, Hb 8.4g/dl, Ht 28.5%, Plat $19.8 \times 10^5$/mm³</td>
<td></td>
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<tr>
<td>WBC 6,900/mm³ (st. 1, seg. 74, lym. 18, eo. 1, ba. 3, mo. 3)</td>
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<tr>
<td>TP 6.14g/dl, Alb. 3.75g/dl, T-bil 0.62mg/dl, D-bil 0.25mg/dl</td>
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<tr>
<td>GOT 19KU, GPT 17KU, LDH 459U, ALP 2.35BLU, FBS 106mg/dl</td>
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<tr>
<td>BUN 42.9mg/dl, CRN 1.70mg/dl, Ccr. 39.4ml/min Na 143.5mEq/l, K 3.7mEq/l, Cl 107.2mEq/l, T-Chol. 212mg/dl</td>
<td></td>
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<tr>
<td>HDL-Chol. 31mg/dl, TG 102mg/dl, ESR 22mm/h, CRP (+)</td>
<td></td>
</tr>
<tr>
<td>CH50 40U/ml, VDRL (-), TPHA (-), HBs-Ag (-), HBs-Ab (-)</td>
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**Arterial Blood Gas analysis**

pH 7.506, Pco₂ 28.2mmHg, Po₂ 63.4mmHg, HCO₃ 22.3

SAT 94.0%, BE -0.0

**Urinalysis**

Specific gravity 1.020, pH 5.5, Sugar (-), Protein 100mg/dl

Occult Blood (-), Sediments; nothing particular

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1987.3.23  
1988.11.9  
11.18

Fig. 1. Sequential chest roentgenograms. Congestive heart failure progressed after hospitalization and was resistant to medical treatments.
Fig. 2. An electrocardiogram showing left ventricular hypertrophy on admission.

Fig. 3. Two dimensional echocardiograms revealed no vegetation of the aortic valve but deformity and insufficient closure in diastole (upper).
Color flow imaging showed severe aortic regurgitation which progressed after hospitalization (lower).

Fig. 4. Clinical course of the patient. PCG, benzylpenicillin; SB-PC, sulbenicillin; CZON, cefuzonam; FMOX, flomoxef; DOA, dopamine hydrochloride; DOB, dobutamine hydrochloride; HD, hemodialysis; E-COM, extra-corporeal ultrafiltration method; ESR, erythrocyte sedimentation rate; WBC, white blood cell; B.T., body temperature; CTR, cardio-thoracic ratio.
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valve exhibited deformity and an increase in echo intensity, which was accompanied by insufficient valvular closure in diastole in the short axis view. Aortic regurgitation (grade 4) was observed on color flow imaging, and the aortic valvular deformity and regurgitation progressed after hospitalization (Fig. 3). The color flow imaging also revealed moderate mitral regurgitation. The mitral valve, however, did not show deformity, calcification or prolapse.

From the time of admission, as shown in Fig. 4, catecholamines such as dopamine and dobutamine and diuretics were employed for treating congestive heart failure, and antibiotics including $1,200 \times 10^4$ units of benzylpenicillin per day were injected for suspected infective endocarditis. Although congestive heart failure was transiently recovered with the use of antibiotics and extra-corporeal ultrafiltration method (ECUM), unconsciousness occurred suddenly, followed by cardiopulmonary arrest which lead to death on December 12.

The gross anatomicopathological findings showed destruction of the aortic valve accompanied by a small vegetation ($2 \times 3 \times 3$ mm). The hematoxylin-eosin stained histological findings of the vegetation revealed precipitated fibrin suggesting the presence of previous inflammation, without definite bacteria (Fig. 5). Multiple cerebral infarction was also found (Fig. 6). The renal artery which had been transplanted from a 21-year-old man, and

Fig. 5. Destruction of the aortic valve accompanied by a small vegetation. Histological findings revealed precipitated fibrin without definite bacteria (hematoxylin-eosin stain, $\times 400$).

Fig. 6. Multiple cerebral infarction, thought to be due to emboli from the vegetation, was found.
the abdominal aorta showed severe progression of atherosclerosis (Fig. 7). A severe coronary stenosis due to atherosclerosis was seen at the proximal portion of the left anterior descending coronary artery. There were no abnormal findings in the transplanted kidney itself.

**DISCUSSION**

Although the use of immunosuppressants has decreased the frequency of rejective reaction in recipients and leads to an improved success ratio in organ transplantation, the increase in infectious disease has posed a new problem, resulting in highest cause of death in the early and late phase of the post-transplantation period (1, 2). The sites of infection in the late phase consist of the urinary tract (29.4%), the respiratory tract (23.0%) and others; the former two contain the prominent lesions. The reported causal organisms are *E. coli*, Klebsiella and Enterobacter for urinary tract infection, and Klebsiella, Enterobacter, Candida albicans, Haemaphilus and Pseudomonas aeruginosa for respiratory infection, in which opportunistic infection is prominent (5, 6). However, cases of infective endocarditis after organ transplantation are rarely reported, and no such reports have been published in Japan (7, 8). Although the reason is unclear, such cases may be included in statistical reports under sepsis. The occurrence of sepsis is more frequent in the early phase of the post-transplantation period, while it occupies 11% of the late phase infections. The causal organisms are mainly Klebsiella, Enterobacter and Pseudomonas aeruginosa (5,6). At present, very few transplantations are being performed in Japan compared with other advanced countries, therefore the cases of endocarditis are few, but would increase with the increase of transplantations.

In the present case, the pathological findings of the vegetation did not show any bacteria within it, and, therefore, diagnostic differentiation from non-bacterial thrombotic endocarditis was required (10). Based on the following, we diagnosed the patient as infective endocarditis with aortic regurgitation with a complication of multiple cerebral emboli: 1) he had a history of odontectomy, 2) he had received immunosuppressants and steroids for 2 yr which easily lead to infection, 3) transient, symptomatic improvement was observed after administration of antibiotics, 4) the destruction of the aortic valve was more severe than that commonly observed in nonbacterial thrombotic endocarditis, 5) nonbacterial thrombotic endocarditis is generally formed under consumptive diseases such as malignant tumors. In the present case, the patient was in good condition in spite of the presence of aortic regurgitation on admission.

It was additionally noted that progression of atherosclerosis was conspicuous on autopsy. Atherosclerosis is hypothesized to be closely related to lipid, thrombus formation, coagulo-fibrinolysis, hemorheology, and viral infection (11). With the long-term administration of steroids, the serum level of cholesterol and triglyceride increase is coupled with a decrease in HDL cholesterol level. Glucose tolerance is also impaired (12, 13). These changes lead to the progression of atherosclerosis. The chronic rejective reaction after transplantation induced vascular inflammation not only in the transplanted renal artery but in systemic arteries and causes injury to vascular endothelial cells and the formation of atherosclerosis (9). The calcified aorta is reported as one of the relative risk factors of infective endocarditis (14). Therefore, the development of atherosclerosis due to transplantation might be the trigger of infective endocarditis in this case.

In the near future, circulatory complications such as high degree atherosclerosis and infective endocarditis will likely increase with the increasing numbers of organ transplantations in Japan. We must elucidate a countermeasure to these complica-
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REFERENCES