

〈Case Report〉

A surgical case of mitral valve replacement for a patient with Fabry disease complicated with hemodialysis

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ABSTRACT Fabry disease is a rare genetic disease, and surgical reports for the patients with Fabry disease are also rarer.

A 58-year-old man presented with chest pain. At the age of 40, he commenced dialysis due to chronic renal failure and at the age of 50, he developed shortness of breath on exertion, and echocardiography showed mitral regurgitation and left ventricular hypertrophy. He was then diagnosed with Fabry disease due to decreased alpha-galactosidase activity. This diagnosis led to enzyme replacement therapy (ERT). The ERT was effective as he had not never experienced further exacerbation of congestive heart failure. While the CHF was put under control, his mitral stenosis gradually worsened, and the patient began to have more chest pain and became hypotensive. He then referred to our section for mitral valve replacement. His mitral annulus was severely calcified and we removed mitral annulus calcification (MAC) at minimum so that we could stitch needles and implanted mechanical valve. Paroxysmal atrial fibrillation and bradycardia made his hemodynamics unstable against ERT, which also caused low dialysis efficiency. It took longer than usual to wean him off catecholamines. His hemodynamics became more stable and dialysis efficiency generally improved, so he moved from ICU to ward on postoperative day 11. On day 32, he was transferred back to the referring hospital for his rehabilitation.

We have reported a surgical case of Fabry disease, that are not only rare but have high perioperative risk due to Fabry disease's specific complications.

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Key words : Mitral stenosis, Fabry disease, Mitral valve replacement, Enzyme replacement therapy

BACKGROUND

Fabry disease is a rare genetic disease caused

by a deficiency of alpha-galactosidase which catalyzes lysosomes. An accumulation of

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globotriaosylceramide due to the lack of alpha-galactosidase produces various disorders. Most cases have peripheral neuropathy beginning in early childhood, and proteinuria gradually emerges. A decline of renal function, cardiomegaly and diastolic dysfunction usually occur in adulthood. Finally, most patients have renal failure and/or heart failure¹⁾.

Some valvular diseases associate with Fabry disease. Some cases of aortic regurgitation (AR) and mitral regurgitation (MR) were reported^{1, 2)}. We report here on a case of mitral stenosis with Fabry disease in which mitral valve replacement was performed. We believe a first case with this special condition.

CASE REPORT

A 58-year-old man presented with chest pain. He had a long history of medical problems leading up to his complaint. He did not know obvious family history. When he was 4 years old, he underwent a left nephrectomy. Then at the age of 40, he commenced dialysis due to progression of renal failure. At the age of 50, he developed shortness of breath on exertion, and echocardiography showed mitral regurgitation and left ventricular hypertrophy. He was then diagnosed with Fabry disease due to decreasing of alpha-galactosidase activity. This diagnosis led to enzyme replacement therapy (ERT). He had been infused agalsidase alfa 3.5mg once

two weeks since his diagnosis was made. The ERT was effective as he had not experienced further exacerbation of congestive heart failure (CHF). While the CHF was put under control, his mitral stenosis gradually worsened, and the patient began to have more chest pain and became hypotensive. He was taking pain-relieving drugs and even narcotic analgesics such as carbamazepine and renorphine due to severe pain in his extremities since childhood. He had a diastolic heart murmur at the apex. There was a internal shunt in his left forearm.

Blood tests showed his hemoglobin was 10.1 g/dL, creatinine was 11.57 mg/dL, urea nitrogen was 79 mg/dL, brain natriuretic peptide was 342.8 pg/ml, and his galactosidase activity was 0.064 nmole/ml (low activity). The other blood test results are shown in Table 1.

An electrocardiogram showed a sinus rhythm of 78 beats per minute and nothing else of significance. Posteroanterior radiograms of the chest showed that the cardiac silhouette was not enlarged and there were no findings to suggest pulmonary edema or pleural effusion. There was massive MAC.

Transepophageal echocardiography showed severe mitral stenosis with a mitral valve area of 0.8 cm², and massive MAC. Other data from the transthoracic echocardiography (Fig. 1) showed a left ventricular diameter (LVD) of 40 mm (diastolic) and 27 mm (systolic), Interventricular septum (IVS) of 12 mm,

Table 1. Blood test results of this patient on admission

WBC	5.51 10 ³ /μL	TP	5.1 g/dL	CK	41 U/L
RBC	3.26 10 ⁶ /μL	Alb	3.3 g/dL	Na	140 mmol/L
Hb	10.1 g/dL	T-Bil	0.4 mg/dL	K	4.4 mmol/L
HCT	29.5 %	ALP	341 U/L	Cl	106 mmol/L
PLT	34.2 10 ³ /μL	γGTP	56 U/L	P	6.4 mg/dL
PT-sec	12.0 sec	LD	144 U/L	Ca	7.6 mg/dL
APTT	29.8 sec	ChE	360 U/L	Mg	1.9 mg/dL
Fib	294 mg/dL	ALT	13 U/L		
AT-III	77.5 %	AST	15 U/L	HbA1c	5.3 %
		Cre	11.57 mg/dL	BNP	342.8 pg/ml
CRP	0.24 mg/dL	BUN	79 mg/dL		
		UA	8.2 mg/dL		

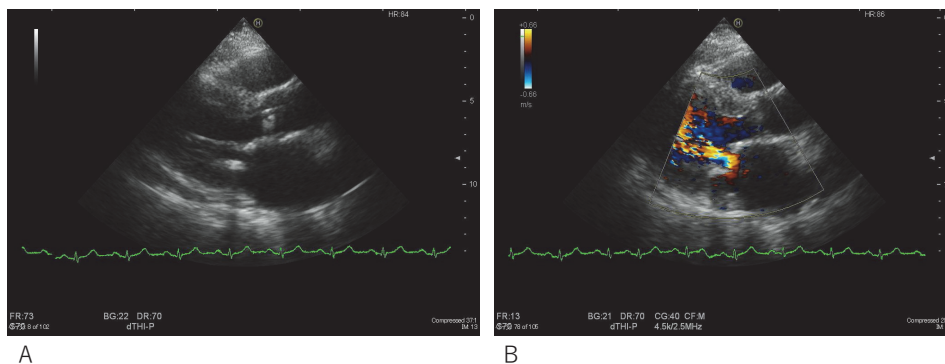


Fig. 1. transthoracic echocardiography

A: parasternal long axis view

B: parasternal long axis view with Doppler
LVH, mitral valve calcification, diastolic mitral jet

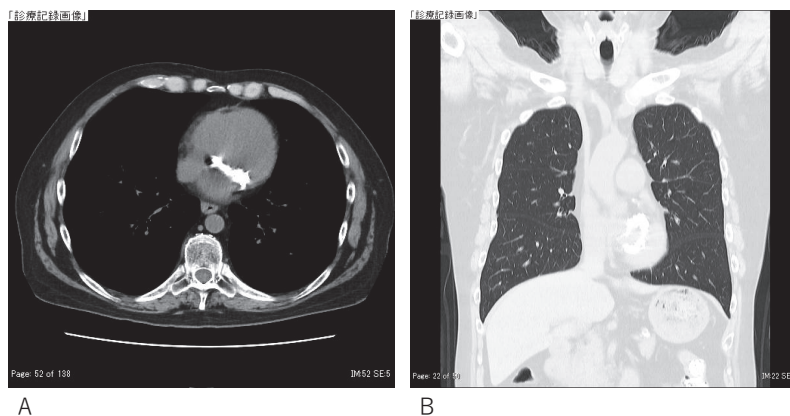


Fig. 2. computed tomography shows severe mitral annulus calcification without pulmonary edema or pleural effusion

posterior wall (PW) of 13 mm, a left ventricular ejection fraction (LVEF) of 65%, an E/A ratio of 0.5, an e/e' ratio of 28.7, a deceleration time of 979 ms and a Tricuspid regurgitation pressure gradient (TRPG) of 30mmHg. Coronary angiography showed no significant stenosis. His right coronary artery was originated from left Valsalva sinus. Computed tomography showed MAC at almost entire circle (Fig.2).

Magnetic resonance imaging of brain showed some previous lacunar infarctions. We did not take MRI image of the heart.

A cardiopulmonary bypass (CPB) via a median sternotomy was established under blood supply to the ascending aorta and bicaval drainage. A left ventricular venting tube was placed in the right superior pulmonary vein. The ascending aorta was clamped and antegrade cardioplegia was administered. Then the left atrium was opened at the interatrial groove. MAC at anterior leaflet was mild, and so we could resect anterior leaflet entirely. MAC at posterior leaflet was marked, then we removed its MAC with a cavitron ultrasonic surgical aspirator (Fig.3). The removal of MAC at posterior

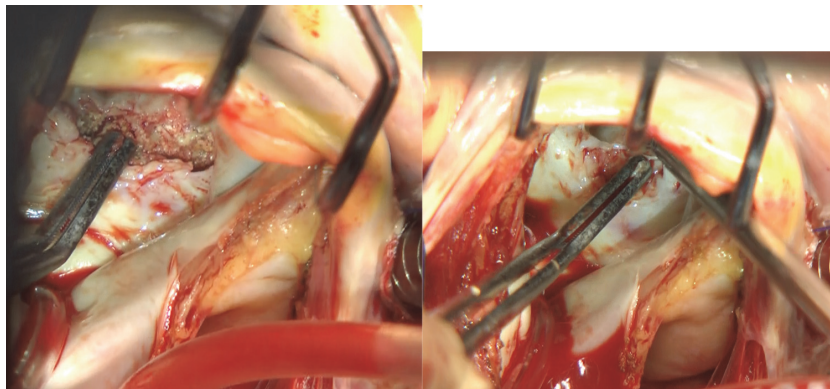
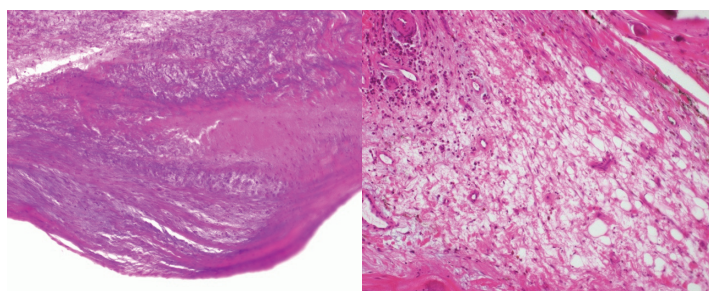
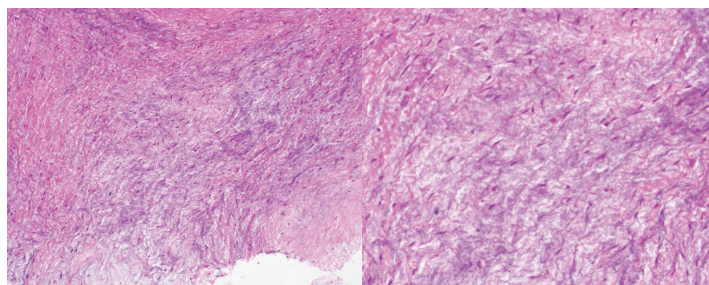


Fig. 3. Mitral valve operative view
Removing mitral annulus calcification



A



B

Fig. 4.

A: mitral valve anterior cusp myxomatous changes and calcification

B: mitral valve posterior cusp myxomatous changes partly calcification

leaflet was so minimum that the needles could stitch through the annulus. Then a mechanical valve (25 mm St. Jude mechanical prosthesis) was implanted in an intra-annular position. The CPB was easily weaned off, and transesophageal echocardiography showed none of perivalvular leakage. Microscopic examination showed that the excised leaflet was

composed of hyaline, myxomatous changes and massive calcification (Fig.4).

The patient was extubated on postoperative day (POD) 1, and continuous hemodiafiltration was commenced on POD 2. Paroxysmal atrial fibrillation and bradycardia made his hemodynamics unstable against ERT, which also caused low dialysis

efficiency. It took longer than usual to wean him off catecholamines. His hemodynamics became more stable and dialysis efficiency generally improved. So he moved from ICU to ward on POD 11. On POD 32, he was transferred back to the referring hospital for his rehabilitation.

Postoperative transthoracic echocardiography showed normal function of mechanical valve leaflets without paravalvular leakage. His parameters were a LVD of 38mm (diastolic) and 24 mm (systolic), IVS of 12 mm, PW of 13 mm, a LVEF of 67%, an E/A ratio of 4.4, an e/e' ratio of 41.6 and a deceleration time of 155 ms and a TRPG of 27 mmHg.

DISCUSSION

Fabry disease is an X-linked genetic disorder. An accumulation of ceramide trihexoside (CD77) in the skin, peripheral nerves, the heart, blood vessels, the kidneys and the brain due to the absence of alpha-galactosidase causes diverse symptoms¹⁾. Clinical diagnosis for Fabry disease is difficult due to its rarity. Most patients have had peripheral neuropathy and dyshidrosis since childhood. After reaching adulthood, renal dysfunction, cardiac dysfunction and valvular diseases progress. Some patients get finally end-stage renal failure, systolic and diastolic cardiac dysfunction with/without heart failure¹⁾. In this case, the patient had peripheral neuropathy, gradually progressing renal dysfunction, left ventricular hypertrophy and valvular disease. His symptoms fit the criteria for a classic case of Fabry disease.

Enzyme replacement therapy (ERT) can improve the prognosis of Fabry disease, especially when applied before the beginning of renal or heart failure. Beck *et al.*³⁾ reported that agalsidase alfa slowed the progression of renal dysfunction and cardiomyopathy, and also slowed the development of complications and death. Kampmann *et al.* reported⁴⁾ on 10 years effects of ERT, and concluded that ERT improved the New York Heart

Association (NYHA) Classification for heart failure for most patients with Fabry disease. In this case, his NYHA Classification clearly improved after beginning ERT.

Some patients with Fabry disease have valvular diseases, mostly aortic regurgitation and/or mitral regurgitation, with rare cases of aortic stenosis. Weidemann *et al.*²⁾ reported on cases of valvular disease associated with Fabry disease. Of 111 patients with Fabry disease, 59 patients had mitral regurgitation (57 mild, 2 moderate), while 18 had aortic regurgitation (17 mild, 1 moderate). There were also 2 cases of aortic stenosis but no cases of mitral stenosis. There are no previous report of mitral stenosis with a patient of Fabry disease and also no previous surgical case reports of such a condition. Our case had mild MR and mild AR, which did not progress after the introduction of ERT. However, the mitral stenosis became severe. We believe the progression of mitral stenosis from atherosclerotic calcification was due to a long history of hemodialysis on the mitral valve along with myxomatous changes associated with Fabry disease which caused mitral regurgitation (Fig. 4).

There are some reports on surgical interventions for Fabry disease complications including mitral valve repair, aortic valve replacement, coronary artery bypass grafting and heart transplantation⁵⁻⁸⁾. There are no previous reports about surgical intervention for mitral stenosis of a patient with Fabry disease. Some reports showed valvular myxomatous degradation similar to our case^{5, 6)}.

Patients with Fabry disease may have atrial, ventricular or bradycardiac arrhythmias⁹⁾. Our case had a history of exacerbation of congestive heart failure triggered by atrial fibrillation and he was performed a catheter ablation at the referring hospital. Even so, it took a long time to stabilize his postoperative hemodynamic status due to paroxysmal atrial fibrillation and bradycardia.

Though we could not take myocardial biopsy, it

was reported that there is marked vacuolation within the cytoplasm of cardiomyocytes, and electron microscopy demonstrates dense lamellar deposits of globotriaosylceramide within lysosomes. And it also reported interstitial fibrosis was evident with a subepicardial or mid-wall pattern of fibrosis, it became more extensive in the posterolateral basal portion of the left ventricle, but myocardial scarring is not commonly associated with aneurysm formation¹⁰.

Left ventricular hypertrophy, together with diastolic and systolic dysfunction, make the postoperative management difficult. Toda *et al.*¹¹ reported that diastolic dysfunction is one specific cause of cardiomyocyte injury. Merello *et al.*¹² reported that in patients who received a coronary artery bypass grafting (CABG), diastolic dysfunction with an E/A ratio > 1.5 and an early filling deceleration time < 150 ms actually have a higher risk of morbidity and mortality than the risk shown by both the Euroscore and Parsonnet score risk models. Severe diastolic dysfunction is a predictive factor of adverse postoperative events. The Euroscore and Parsonnet score risk models may not accurately reflect some important risk factors.

In this case, a preoperative echocardiography showed an E/A ratio of 0.5, an e/e' ratio of 28.7, however a postoperative echocardiography showed an E/A ratio of 4.4, an e/e' ratio of 41.6. The preoperative result did not directly mean as diastolic dysfunction due to mitral stenosis. The postoperative echocardiography meant that he had grade I diastolic dysfunction as defined by the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines¹³. Even though his preoperative Euroscore was only 3.83, postoperative hemodynamic instability which needed catecholamines longer and refractory arrhythmias revealed that he actually had a higher risk than initially indicated.

It might seem that the postoperative course of this

case was similar to the patients with severe MAC and chronic atrial fibrillation without Fabry disease. We think it was because ERT stabilized heart failure of this patient. There is a great difference in surgical risks between the patients with preoperative heart failure and the patients without it. So, the perioperative approaches have a great difference between them. ERT could possibly lower the surgical risk if the surgical case was with Fabry disease.

There were 0.9- 4.0% of patients who were diagnosed as Fabry disease from the patients who were clinically diagnosed as hypertrophic cardiomyopathy or left ventricular hypertrophy^{14, 15}. We might meet patients with Fabry disease actually more than we have known. And the emerge of ERT have those patients live longer and could cause valvular stenosis as had happened to this case. There may be more patients of mitral stenosis with hemodialysis who actually has Fabry disease.

CONCLUSIONS

We experienced a rare surgical case of mitral stenosis for a patient with Fabry disease complicated with hemodialysis. The risk of surgery is suspected to be higher than the established risk model calculations due to the characteristics of cardiomyopathy and arrhythmia. It should be sure that the patients with Fabry disease has commenced on ERT before the surgery to stabilize their heart failure and to lower the surgical risks.

ABBREVIATIONS

AR: Aortic regurgitation, MR: mitral regurgitation, ERT: enzyme replacement therapy, CHF: congestive heart failure, LVD: left ventricular diameter, IVS: Interventricular septum, PW: posterior wall, LVEF: left ventricular ejection fraction, TRPG: Tricuspid regurgitation pressure gradient, CPB: cardiopulmonary bypass, POD: postoperative day, NYHA: New York Heart Associations, CABG:

coronary artery bypass grafting.

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