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【 CASE REPORT 】

Fabry Disease on Peritoneal Dialysis with Cardiac Involvement

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Abstract:
Fabry disease (FD) is an X-linked lysosomal storage disorder resulting from a lack of alpha-galactosidase A (AGALA) activity in lysosomes. We herein report a patient with FD revealed by a renal biopsy who survived seven years after the introduction of peritoneal dialysis despite having severe heart failure due to left ventricular hypertrophy (LVH). FD was diagnosed based on a renal biopsy and biochemical analysis showing a low enzymatic activity of AGALA. A microscopic examination at the autopsy revealed marked hypertrophy and vacuolation of cardiac muscle cells. In our case, cardiac involvement determined the prognosis. Peritoneal dialysis is the modality of choice in the long-term management of dialysis patients with FD.

Key words: Fabry disease, left ventricular hypertrophy, Zebra body, peritoneal dialysis

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Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder resulting in cellular dysfunction caused by pathogenic variants in the alpha-galactosidase A (AGALA) gene mapped to the long arm (Xq22.1 region) of the X chromosome (1). Progressive accumulation of globotriaosylceramide (Gb3) in cells throughout the body leads to various clinical manifestations and consequently major organ failure (2).

Progressive nephropathy is a main feature of FD. Although some clinical signs of Fabry nephropathy such as proteinuria, are already present in childhood (being noted in approximately 50% by 35 years old and 90% by 50 years old), patients are often diagnosed relatively late in the course of the disease (3). The prevalence of FD in dialysis populations has been examined in several studies, most of which report <1% of hemodialysis patients as having gene mutations (4-6). The majority of patients with FD have cardiac involvement that mainly manifests as left ventricular hypertrophy (LVH) (7), which makes the management of dialysis therapy complicated.

We herein report the case of a man who developed end-stage renal disease (ESRD) with a restricted cardiac function due to LVH caused by FD. We describe the clinical course and pathological findings.

Case Report

A 56-year-old man was referred to our department for proteinuria. His medical history included hypohidrosis, and he had a family history of LVH in his mother and brother.

The only symptom he declared was an occasional unknown fever that had existed for 20 years. A physical examination revealed an arterial blood pressure of 121/60 mmHg, a heart rate of 70 bpm, normal oxygen saturation, a slightly high body temperature of 37.5℃, a discreet systolic murmur, and bilateral non-pitting edema. An electrocardiogram showed a regular sinus rhythm with a normal PR interval and LVH of 40 mm assessed using the Sokolow-Lyon index [S-wave voltage in V1+R-wave voltage in V5 or V6 (whichever is larger) >35 mm]. An echocardiogram showed

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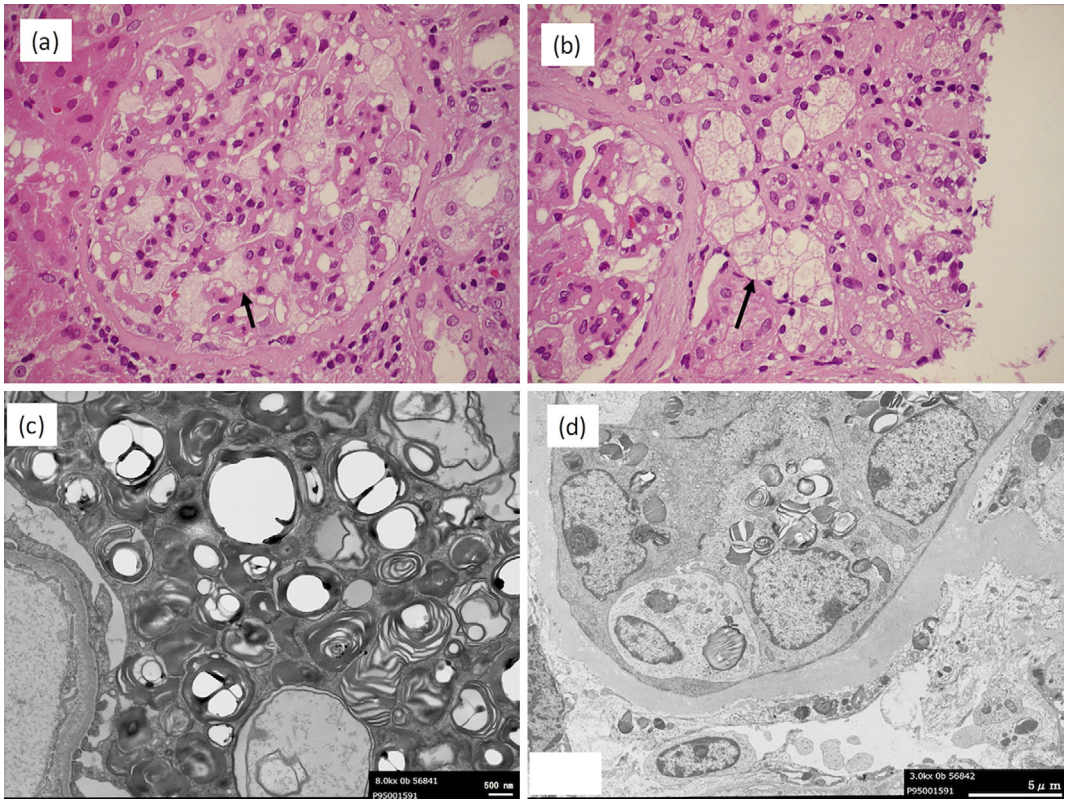

Figure 1. **a: Light microscopy shows extensive inclusion bodies of glycolipid in foamy podocytes. b: Foamy cells (vacuolation) were also present among tubular epithelial cells. c: Electron microscopy shows Zebra bodies packed with lamellated membrane structures in podocytes. d: Zebra bodies were noted on the tubule.**

concentric LVH with interventricular septal thickness of 24 mm and posterior wall thickness of 22 mm. The left ventricular ejection fraction (LVEF) was 76%.

Laboratory findings were as follows: serum urea nitrogen level was 23.0 mg/dL, creatinine 1.8 mg/dL (glomerular filtration rate estimated by the Cockcroft-Gault formula: 51.8 mL/min), Immunoglobulin (Ig)G 1,260 mg/dL, IgA 192 mg/dL, IgM 172 mg/dL, proteinuria of 1.32 g/24 hours, and hematuria of 1-5 red blood cells (RBCs)/high-power field (HPF). We performed a renal biopsy. Global sclerosis observed via light microscopy (LM) was present in 15 out of 28 glomeruli. The preserved glomeruli showed extensive inclusion bodies of glycolipid in foamy podocytes and mesangial widening (Fig. 1a). Vacuolation was also present in tubular epithelial cells (Fig. 1b). Immunofluorescence microscopy demonstrated weak mesangial positive staining for IgM. An electron microscopic examination revealed Zebra bodies packed with lamellated membrane structures on the podocytes (Fig. 1c) and tubule (Fig. 1d). The diagnosis of FD was confirmed by a low AGALA activity of 0.9 nmol/mg protein/h (normal: 33.4-134). Our patient did not agree to a gene mutation test or enzyme replacement therapy.

Although the renal function remained unchanged, proteinuria continued to increase and reached 3.83 g/24 hours during his first year of follow-up. The urinary protein excretion continued to increase and ranged between 3.52 to 5.74 g/24 hours in the course of pre-dialysis follow-up. With such a gradual deterioration of his renal function, it took three years after his initial visit to reach ESRD.

During follow-up visits, he presented with impaired cognition and nausea derived from uremia, which required renal replacement therapy. For ESRD patients with concomitant heart failure, continuous ambulatory peritoneal dialysis (CAPD) has been reported to be associated with better outcomes than hemodialysis (8, 9). As the management of heart failure seemed difficult due to treatment resistance and intolerance of conventional therapy, we chose CAPD as an alternative therapy. At the initiation of CAPD, electrocardiographic findings revealed bradycardia of HR 50 bpm with non-sustained ventricular tachycardia. In addition, the PR interval was relatively short at 100 ms, and severe LVH of 62 mm by the Sokolow-Lyon index was noted. Echocardiogram findings showed severe concentric LVH with a globally increased left ventricular wall thickness of 26 mm. However, despite the progressed LVH, the LVEF was 66% and relatively well preserved.

He started CAPD with a regimen comprising of 1.5% dextrose (Dianeal-N PD-4 1.5%; Baxter, Tokyo, Japan)×1.5 L×3+2.5% dextrose×1.5 L×1, and the daily ultrafiltration amount was 600-800 mL/day. After the first 4 years with an uneventful clinical course, a gradual decrease in the ultrafiltration volume led to a change in his CAPD regimen to 1.5% dextrose×1.5 L×3+2.5% dextrose×1.5 L×2. For the next year and a half, the daily ultrafiltration volume was sta-

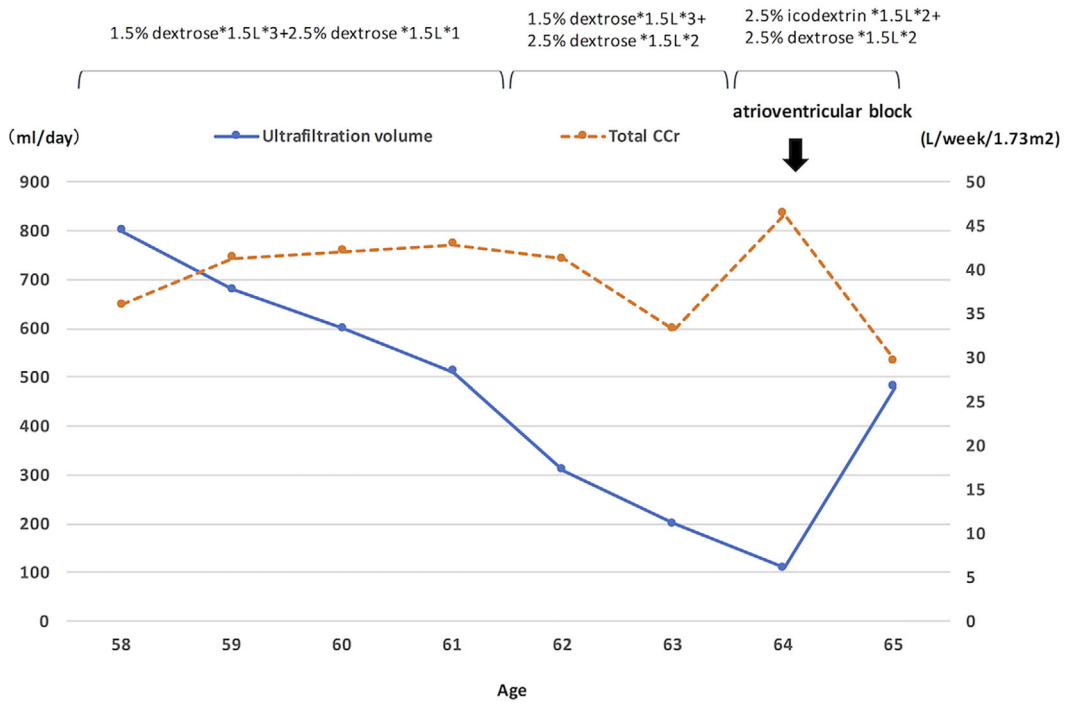

Figure 2. **The patient's clinical course.**

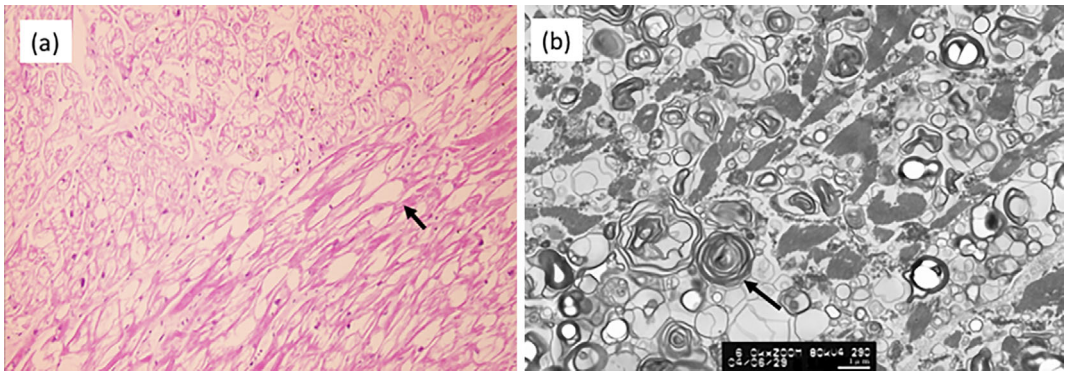

Figure 3. **a: LM showed vacuolization on almost all myocytes throughout both ventricles and atria. b: EM showed myelin-like structures within myocytes. LM: light microscopy, EM: electron microscopy**

ble around 100-500 mL/day, however, cardiac enlargement on chest X-ray to CTR57% and gradually gaining weight, his CAPD regimen was again changed to 2.5% icodextrin (Exraneal; Baxter)×1.5 L×2+2.5% dextrose×1.5 L×2. Subsequently, third-degree atrioventricular block as well as non-sustained ventricular tachycardia began to present on an electrocardiogram, so a DDD mode pacemaker was implanted.

While the D/P creatinine ranged between 0.69-0.73 over 5 years, it subsequently reached a high solute D/P of 0.82. The echo-graphically estimated ejection fraction (EF) was <30% and showed clinical signs of congenital heart failure. Although the daily ultrafiltration volume increased to 480-780 mL/day temporarily, persistent low cardiac output made it difficult to generate sustained ultrafiltration (Fig. 2). His blood pressure was maintained throughout the clinical course. One morning, seven years after the initiation of CAPD treatment, he was found dead in bed. An autopsy was conducted at our hospital for a further evaluation.

Autopsied Specimen

Macroscopic findings at the autopsy showed pleural effusion (right: 340 mL, left: 570 mL), renal atrophy (right: 80 g, left: 70 g), marked cardiac hypertrophy (heart weight: 715 g), significant ventricular wall thickening (LV thickness: 33 mm, RV thickness: 12 mm), and cerebral ischemic changes with no signs of stroke or hemorrhaging. Microscopically, the renal histological findings revealed the disappearance of almost all glomeruli and vacuolization in the tubular epithelial cells. As at the previous renal biopsy, myelin-like structures were detected in podocytes and glomerular endothelial cells using electron microscopy. Al-

most all myocytes throughout both ventricles and atria showed vacuolization (Fig. 3a), and electron microscopy showed myelin-like structures within myocytes (Fig. 3b). There was no vacuolization in the endothelial cells or smooth muscle cells of the coronary arteries. Limited accumulation was observed in the electrical conduction tissues and liver. Regarding the peritoneum, there were no findings of calcifications, intestinal encapsulation, cellular infiltrates, or fibrosis.

Discussion

There have been many reports regarding the pathophysiology of FD. However, few studies have reported on its clinical course in dialysis patients and the relevant histological findings. In our patient, the progression of cardiac involvement of FD determined the prognosis. As previously reported, cardiac involvement of FD is associated with significant morbidity and early death due to heart failure or ventricular arrhythmias (10-12). In our case, autopsy findings showed global cerebral ischemia with no signs of occlusion or hemorrhaging, which implies the existence of severe hypotension and hypoventilation over a prolonged period of time. Given his marked concentric LVH, terminal heart failure likely caused sudden cardiac death. As an alternative cause of sudden cardiac death, conduction tissue infiltration with glycosphingolipids may also have caused electric instability, appearing as ventricular arrhythmia.

The plasma level of globotriaosylsphingosine (lyso-Gb3), a deacylated metabolite of Gb3, is speculated to play a role in the progression of LVH (13). Thus, enzyme replacement therapy (ERT), which has now become a key treatment for FD, is expected to help delay the progression of FD by clearing Gb3 deposits in microvascular endothelial cells. The European Fabry Working Group reported a consensus that ERT should not be withheld from patients with severe renal insufficiency (glomerular filtration rate <45 mL/min/1.73 m^2) or from those on dialysis (14). Although some studies have reported the limited effectiveness of ERT for patients who show some specific features of advanced diseases, such as cardiac fibrosis or severe renal dysfunction with overt proteinuria (14, 15), no studies have given an unequivocal answer concerning a cut-off value. A better prognosis may therefore have been achieved if our patient had initiated ERT at the diagnosis of FD, before irreversible organ changes occurred.

Electron microscopy at the autopsy demonstrated abundant Zebra bodies packed with lamellated myelin-like inclusions in podocytes and glomerular endothelial cells as well as in myocytes. The origin of these inclusions is unclear, but they are thought to be remnants of damaged endothelial cells and necrotic smooth muscle cells (16).

In our case, by choosing peritoneal dialysis instead of hemodialysis, gentle removal of retained water without sudden changes in extracellular volume prevented the development of hypotension and enabled sustainable fluid removal. The majority of long-term peritoneal dialysis patients develop reduction of both free water transport and small-pore fluid transport caused by fibrosis and vaculopathy; however, our patient did not show such peritoneal structural abnormalities. Therefore, cardiac failure caused by the progression of LVH is considered the main cause of ultrafiltration on CAPD.

In conclusion, this is an autopsied case of FD with renal and cardiac involvement with a survival of seven years after the introduction of peritoneal dialysis. Progression of cardiac involvement, such as LVH and the occurrence of ventricular arrhythmia, seemed to determine the prognosis. Peritoneal dialysis may be the modality of choice in the long-term management of dialysis patients with FD.

The authors state that they have no Conflict of Interest (COI).

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