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Case Report

Massive accumulation of globotriaosylceramide in various tissues from a Fabry patient with a high antibody titer against alpha-galactosidase A after 6 years of enzyme replacement therapy

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ABSTRACT

Fabry disease is an X-linked metabolic disorder due to a pathogenic mutation of the GLA gene. The accumulation of globotriaosylceramide (Gb3) damages multiple organs, including the heart, kidney and nervous system, especially in classical type Fabry disease. Enzyme replacement therapy (ERT) using recombinant alpha-galactosidase A has been shown to remove Gb3 from organs and to improve the prognosis of Fabry disease. We herein report the case of a 67-year-old classical type Fabry patient who had been treated with ERT for 6 years and who continuously showed a high antibody titer against recombinant alpha-galactosidase A during therapy. A post-mortem examination was performed after sudden death. A histological examination revealed the massive accumulation of Gb3 in various organs, even after long term ERT. In addition to the typical pathological findings as reported in tissue biopsy samples, the serious accumulation of Gb3 in the cardiac conduction system and the endocrine system was detected. Since the start of ERT for this patient might be too late to improve organ damage and prognosis, ERT should be started before the appearance of major organ involvement for the effective elimination of Gb3 and changes in the therapeutic strategy might be considered if the patient shows a high antibody titer against recombinant alpha-galactosidase A.

1. Introduction

Fabry disease is a congenital metabolic disorder that occurs due to the mutation of the gene encoding alpha-galactosidase A (GLA), which is located on the X chromosome [1]. Affected males (hemizygous) show two types of Fabry disease (classical type and late-onset type), whereas affected females (heterozygous) also show the various symptoms as detected in male patients [2]. Classical type male patients have more severe form of Fabry disease symptoms due to the absence or very low residual activity of alpha-galactosidase A. The accumulation of glycosphingolipids (mainly globotriaosylceramide, Gb3) in various organs, including the heart, kidney and nervous system, has been reported [1]. However, few studies have reported the relationship between the accumulation of Gb3 and functional changes, and the accumulation of Gb3 in various organs other than the major affected organs. We had the opportunity to perform a postmortem examination following sudden death of a male classical type Fabry disease patient with major organ involvement (heart failure and hemodialysis) after 6 years of enzyme replacement therapy (ERT). We found the massive accumulation of Gb3 in multiple organs, including the cardiac conduction system and endocrine system, even after long term ERT.

2. Case presentation

A 66-year-old man was admitted to Jikei University hospital complaining of severe dyspnea on exertion. His symptom had been worsening during a few months before his admission and he finally complained of nocturnal orthopnea.

He noticed acroparesthesia and hypohidrosis at 8 years of age. He had also suffered from sudden high fever at 4–5 times per year since

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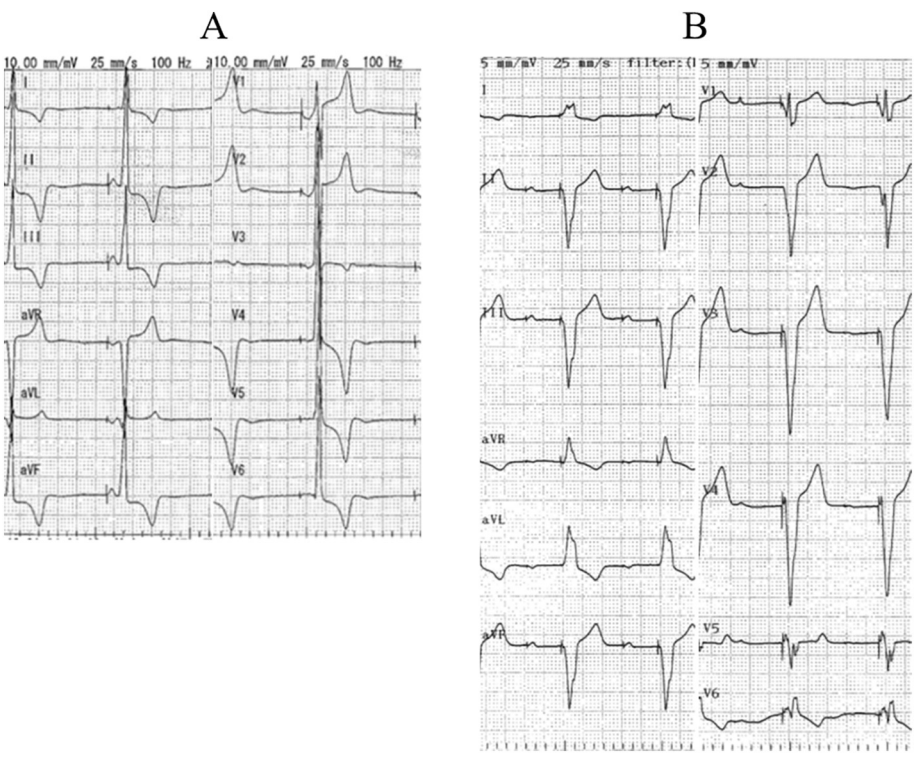

Fig. 1. A. Electrocardiogram at 49 years of age. A dual-chamber pacemaker had been implanted. Atrial pacing and ventricular sensing rhythm with PQ shortening appeared. B. Electrocardiogram at 66 years of age. Atrial pacing and ventricular pacing rhythm with a prolonged PQ interval appeared. Please note that the calibration was half (5 mm/mV) in this electrocardiogram.

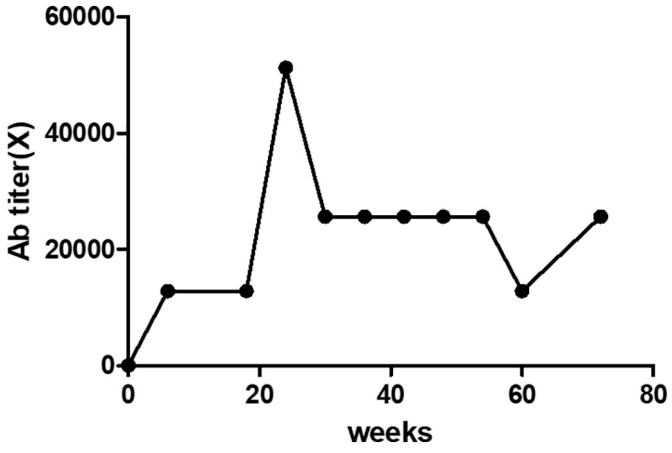

Fig. 2. The time course of antibody titer against agalsidase beta during the term of enzyme replacement therapy. Vertical axis: Arbitrary values of antibody titer against agalsidase. Horizontal axis: Time after the start of enzyme replacement therapy. Ab: antibody.

then. An electrocardiogram abnormality with left ventricular hypertrophy was pointed out at 48 years of age. He suffered from syncope due to an 8-second arrest and he was diagnosed with sick sinus syndrome at 49 years of age, and a dual-chamber pacemaker was implanted. At that time, an electrocardiogram showed atrial pacing with left ventricular hypertrophy and PQ shortening (Fig. 1A). To examine the etiology of cardiac hypertrophy and arrhythmia, cardiac biopsy was performed; based on the examination of the cardiac tissue, Fabry disease was suspected as a possible cause of cardiac hypertrophy. He was then examined with the measurement of the alpha-galactosidase A activity in his white blood cells and was diagnosed with Fabry disease in another University hospital. He came to our hospital to receive enzyme replacement therapy (ERT) using recombinant alpha-galactosidase A (agalsidase beta) at 61 years of age. At that time, a mutation analysis revealed pathological GLA mutation of p.E358del and classical type Fabry disease was confirmed. During the term of ERT, the patient consistently showed a high antibody titer against agalsidase beta (Fig. 2). The antibody titer was determined by an ELISA in Genzyme Corporation. The detailed methods had been described elsewhere [3].

On admission, his pulse rate was 70 bpm with regular rhythm, and his systolic and diastolic blood pressure was 170 mmHg and 112 mmHg, respectively. On auscultation, normal heart sounds were detected and no extra heart sounds or murmurs were detected. Respiratory sounds revealed coarse crackles at the bottom of both lung fields. His lower legs showed pretibial edema on both sides. Laboratory examinations revealed normocytic normochromic anemia with a hemoglobin level of 9.3 g/dl. Blood biochemical tests showed end-stage renal disease (BUN 77 mg/dl, Cr 6.42 mg/dl). His brain natriuretic peptide level was markedly increased (2154.3 pg/ml). His chest X-ray showed pulmonary congestion with an increased cardiothoracic ratio. An electrocardiogram showed an atrial ventricular sequential pacing rhythm of 60 bpm (Fig. 1B). Echocardiography revealed severe concentric hypertrophy with a normal systolic function, however, the diastolic function was severely depressed. The patient was diagnosed with congestive heart failure due to diastolic dysfunction and end-stage renal failure. After admission, he was intensively treated with various medications and hemodialysis was introduced. He was recovered and was discharged, and regularly underwent hemodialysis (three times a week).

At eight months after discharge, he was found dead in his home; he was 67 years of age. Because he underwent hemodialysis on the day before his death, he died within 24 h after his last visit to the clinic. According to his will, his body was transferred to Jikei University hospital for a post-mortem examination.

2.1. Pathological findings

For a histological analysis, the samples were fixed in 10% buffered formalin and paraffin embedded. Sections were stained with Masson trichrome and immunohistochemistry was performed to detect monoclonal anti-Gb3 antibodies (clone BGR23, kind gift from Seikagaku Biobusiness Corporation) (this antibody is now available as A2506 from Tokyo Chemical Industry, Tokyo, Japan) [4]. For transmission electron

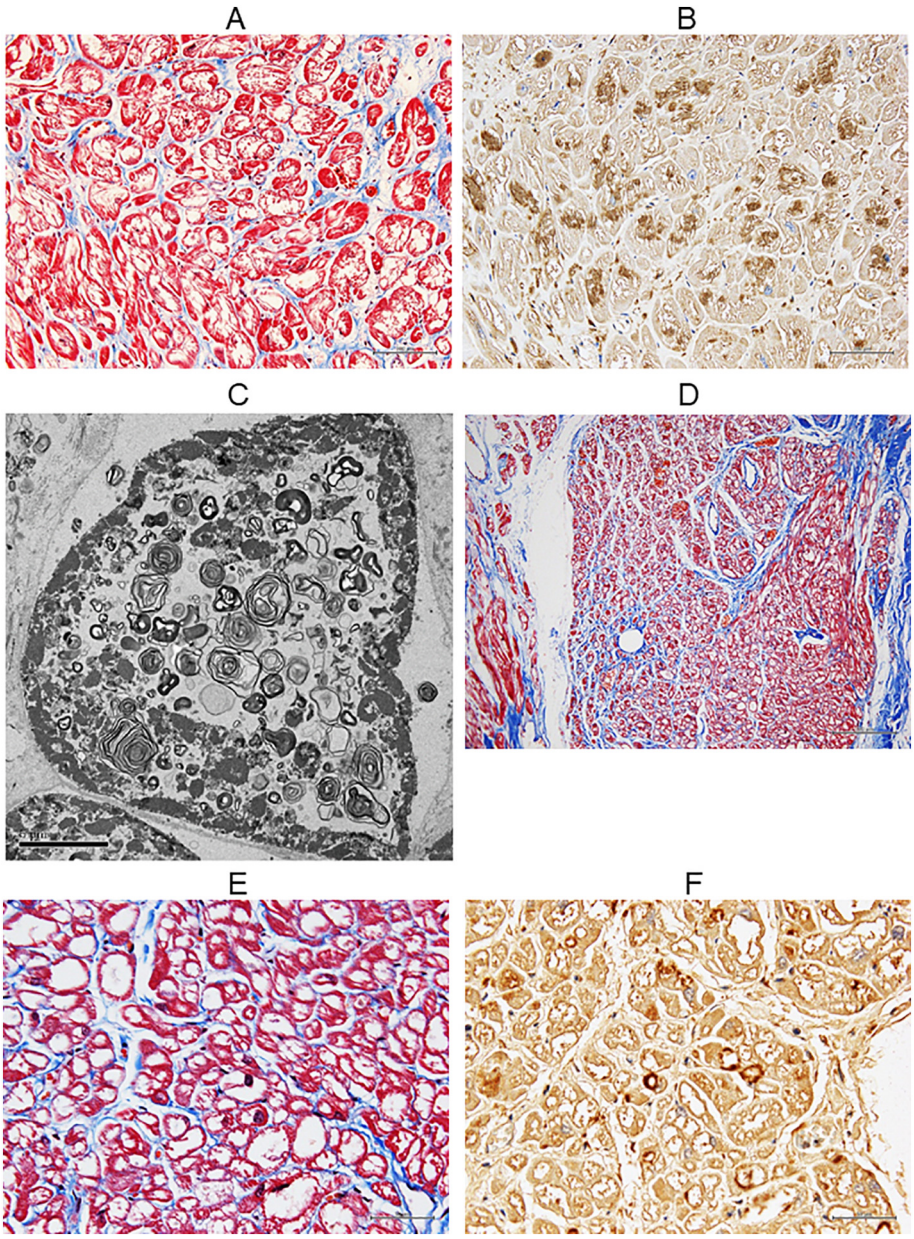

Fig. 3. A. Light microscopic appearance of cardiomyocytes of left ventricular muscle using Masson Trichrome staining (original magnification ×20, scale bar = 100 μm). B. Immunostaining against Gb3 in cardiomyocytes using anti-Gb3 antibody. Brown areas indicate the accumulation of Gb3 (original magnification ×20, scale bar = 100 μm). C. Electron microscopic appearance of cardiomyocytes. Typical zebra bodies were detected into cardiomyocytes (original magnification ×5000, scale bar = 5 μm). D. Low magnification appearance of atrio-ventricular node using Masson Trichrome staining (original magnification ×10, scale bar = 200 μm). E. High magnification appearance of atrio-ventricular node (original magnification ×40, scale bar = 50 μm). F. Immunostaining against Gb3 in atrio-ventricular node using anti-Gb3 antibody. Brown areas indicate the accumulation of Gb3 (original magnification ×40, scale bar = 50 μm).

microscopy, samples were fixed in glutaraldehyde, post fixed in osmium tetroxide. Ultrathin sections were stained with uranyl acetate and lead hydroxide.

An enlarged heart with severe hypertrophy in both ventricles (heart weight, 606 g) was observed. Light microscopy with Masson trichrome staining revealed vacuolization in the cardiomyocytes with interstitial fibrosis in the left ventricular muscle (Fig. 3A). Immunohistochemistry for anti-Gb3 showed the deposition of Gb3 within cardiomyocytes (Fig. 3B). Electron microscopy showed typical zebra bodies inside the cardiomyocytes (Fig. 3C). In atrio-ventricular node, serious vacuolization of the myocytes and significant interstitial fibrosis were also observed (Fig. 3D, E). Immunohistochemistry for anti-Gb3 revealed the deposition of Gb3 within atrio-ventricular nodal myocytes (Fig. 3F). In cardiac tissue, Gb3 staining in vascular endothelial cells is weak compared with the staining in cardiomyocytes.

Both kidneys were atrophied with a thin cortex and mild dilatation of the pelvis (right kidney weight, 78 g; left kidney weight, 79 g). In the glomeruli, light microscopy revealed vacuolization in the epithelial cells (Fig. 4A) which was confirmed as Gb3 deposition by immunohistochemistry for anti-Gb3 antibodies (Fig. 4B). Electron microscopy showed zebra bodies in the epithelial cells (Fig. 4C). In the renal tubules, Gb3 accumulation was identified in distal tubules and the collecting duct, and zebra bodies were also revealed by electron microscopy (Fig. 4D–F). In renal tissue, Gb3 staining in vascular endothelial cells is weak and we could not find inclusion body in vascular endothelial cells by electron microscopy.

Multiple small infarctions were observed in the cerebral cortex, basal ganglia, thalamus and cerebellar hemisphere. In the central nervous system, Gb3 accumulation was mainly observed in the small vessel walls. In the peripheral nervous system, Gb3 was identified in the interstitial tissues of the dorsal root ganglion and nerve root (Fig. 5A, B).

Light microscopy revealed the accumulation of Gb3 in the pituitary gland (Fig. 5C, D) and adrenal gland (Fig. 5E, F). Electron microscopy identified zebra bodies in the pituitary gland (Supplemental Fig. I). There was no accumulation of Gb3 in the thyroid gland or parathyroid gland.

In the aorta, gross observation revealed wall thickness and atherosclerotic changes. Immunohistochemistry and electron microscopy identified Gb3 accumulation, mainly in the smooth muscle cells of the media and scarce accumulation of Gb3 in vascular endothelial cells.

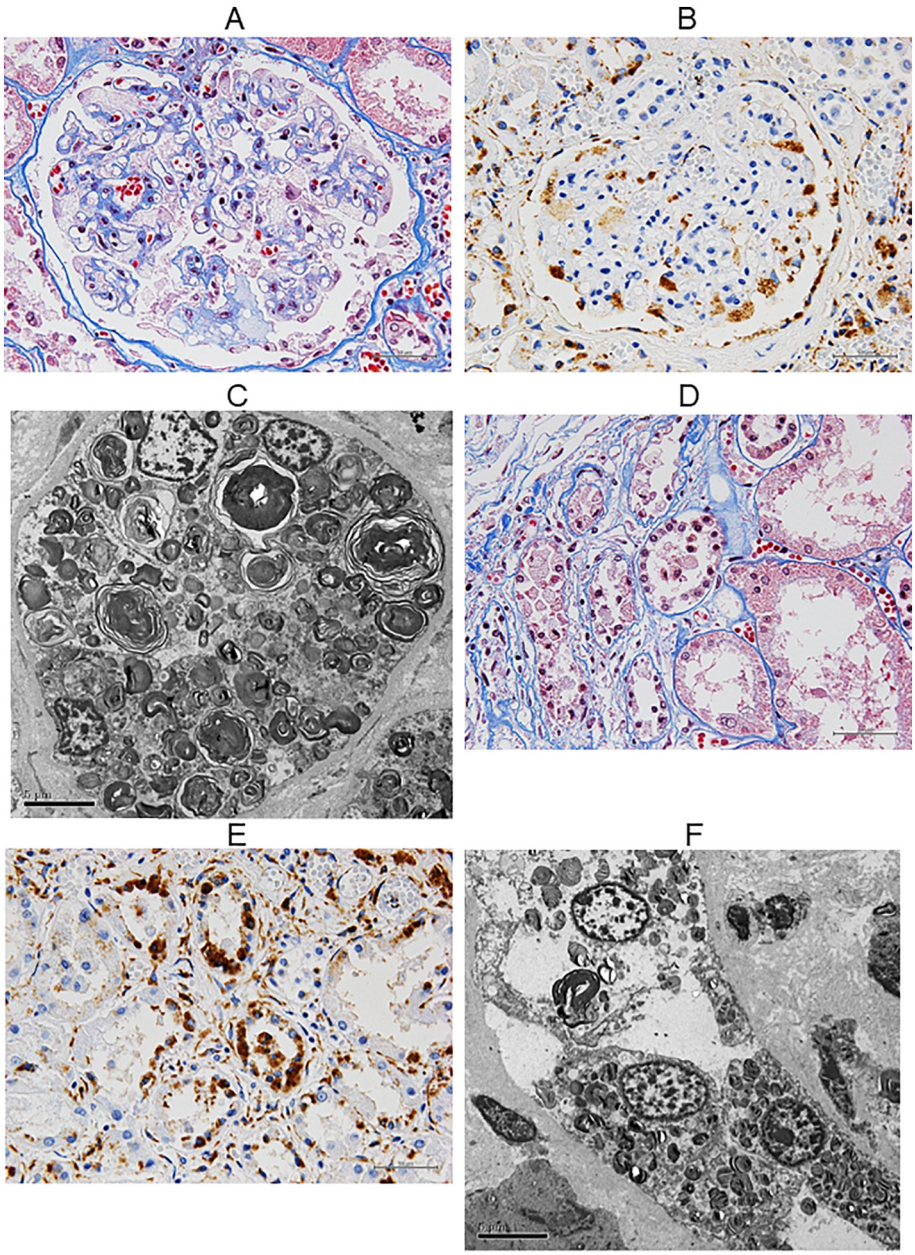

Fig. 4. A. Light microscopic appearance of glomerulus using Masson Trichrome staining (original magnification ×40, scale bar = 50 μm). B. Immunostaining against Gb3 in glomerulus using anti-Gb3 antibody. Brown areas indicate the accumulation of Gb3 (original magnification ×40, scale bar = 50 μm). C. Electron microscopic appearance of glomerulus. Typical zebra bodies were detected into epithelial cells (original magnification ×4000, scale bar = 5 μm). D. Light microscopic appearance of renal tubules (original magnification ×40, scale bar = 50 μm). E. Immunostaining against Gb3 in renal tubules. Brown areas indicate the accumulation of Gb3 (original magnification ×40, scale bar = 50 μm). F. Electron microscopic appearance of renal tubules (original magnification ×4000, scale bar = 5 μm).

Severe congestion combined with alveolar bleeding and fibrin deposition, and focal bronchial pneumonia appeared in both lungs. Severe congestion was also observed in the liver and spleen.

3. Discussion

The post-mortem examination suggested that the cause of death in this patient was heart failure with lethal arrhythmia or respiratory failure with aspiration pneumonia.

To clarify the accumulation of Gb3, we used monoclonal antibody against Gb3 [5]. This antibody was originally tested to determine the accumulation of Gb3 in the rat small intestine using immunostaining and immunohistochemistry [4]. A recent report clarified the use of this antibody in the immunohistochemical detection of Gb3 in the cardiac myocytes of a Fabry disease patient [6]. Previous study also identified cellular and tissue localization of Gb3 in Fabry disease using the same antibody [7]. The pathological examination revealed the massive accumulation of Gb3 in various organs of the body, even after 6 years of ERT. ERT might eliminate the accumulation of Gb3 from various organs [8,9]. However, these cases started ERT at an earlier phase of organ involvement. In the present case, ERT was started at 61 years of age, after the patient already had suffered from cardiac (left ventricular hypertrophy and sick sinus syndrome) and renal (moderate kidney dysfunction) involvement. The application of ERT for elder Fabry patient is still controversial. Some reports indicate no prevention of progression of organ damage and death [10] and criteria for not starting ERT for advanced stage of Fabry disease [11]. In contrast, another report showed that ERT slowed progression of the organ damage and death even in advanced stage of Fabry disease [12]. In addition, previous study reported that 2.5 years of ERT did not appreciably clear storage material in cells other than vascular endothelial cells [13]. Indeed, we found scarce accumulation of Gb3 into vascular endothelial cells in our case. Therefore, the start of ERT for this patient might be too late to improve organ damage and prognosis. In addition, this particular case had substantial level of antibody titer against agalsidase beta during the course of ERT (Fig. 2) which might have reduced the effectiveness of ERT [14]. The neutralizing effect of the antibody against recombinant alpha-galactosidase A has already been reported [15].

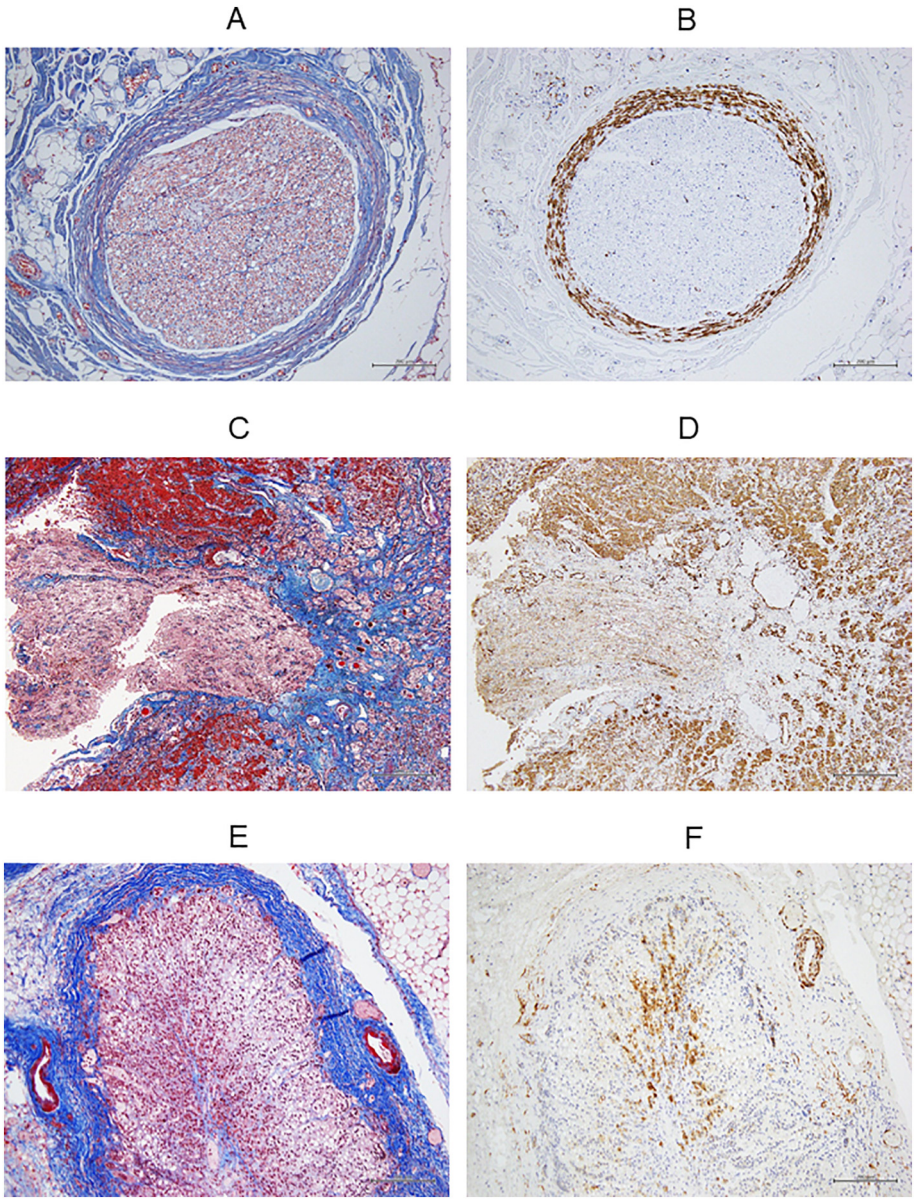

Fig. 5. A. Light microscopic appearance of axillary nerve using Masson Trichrome staining (original magnification ×4, scale bar = 200 μm). B. Immunostaining against Gb3 in axillary nerve using anti-Gb3 antibody. Brown areas indicate the accumulation of Gb3 (original magnification ×4, scale bar = 200 μm). C. Light microscopic appearance of pituitary gland (original magnification ×4, scale bar = 500 μm). D. Immunostaining against Gb3 in pituitary gland using anti-Gb3 antibody. Brown areas indicate the accumulation of Gb3 (original magnification ×4, scale bar = 500 μm). E. Light microscopic appearance of adrenal gland (original magnification ×10, scale bar = 200 μm). F. Immunostaining against Gb3 in adrenal gland using anti-Gb3 antibody. Brown areas indicate the accumulation of Gb3 (original magnification ×10, scale bar = 200 μm).

Thus, starting ERT before the appearance of major organ involvement is necessary for the effective elimination of Gb3 from affected organs. The development of a strategy to reduce the antibody titer against recombinant alpha-galactosidase A, such as in ERT for Pompe disease, might also be considered.

3.1. Heart involvement

The massive accumulation of Gb3 explained the patient's severe biventricular hypertrophy. Additional interstitial fibrosis shows the loss of myocytes, which might be due to inflammatory changes [16]. In this particular patient, the massive accumulation of Gb3 and fibrotic changes were also found in nodal tissues (Fig. 3D–F). Notably, most of the myocytes in the atrio-ventricular node showed the accumulation of Gb3, which could cause acceleration of atrio-ventricular conduction (Fig. 1A) [17]. Further damage of the nodal myocytes and interstitial fibrosis of the nodal tissue could disturb atrio-ventricular conduction, leading to complete atrio-ventricular block (Fig. 1B) [18].

3.2. Renal involvement

The atrophic kidneys showed the terminal stage of renal disease. Severe accumulation of Gb3 in the glomeruli, mainly in epithelial cells, confirmed the disturbance of glomerular filtration function (Fig. 4A–C). In addition, the accumulation of Gb3 in the renal tubular cells indicated tubular reabsorption dysfunction (Fig. 4D–F). Both filtration and reabsorption dysfunction lead to end-stage renal disease, which requires hemodialysis [19].

3.3. Nervous system involvement

In Fabry disease, the involvement of Gb3 accumulation in the central nervous system has not been proven because of the absence of neurological disturbance, which is frequently observed in other congenital metabolic disorders [20]. Instead, the accumulation of Gb3 was detected in the small vessel walls, which could cause cerebrovascular disease, including infarction and transient ischemic attack [21]. In the peripheral nervous system, however, the accumulation of Gb3 in the interstitial tissue of the dorsal root ganglion and nerve root (Fig. 5B) could explain the acroparesthesia and hypohidrosis typically observed

in classical type Fabry disease [22].

3.4. Endocrine system involvement

A previous report suggested that latent endocrine dysfunctions, including adrenal insufficiency, hypothyroidism and reproductive dysfunction, occurred in patients with Fabry disease, although the pathological documentation of the accumulation of Gb3 in the endocrine system was not performed [23]. Our present observation of the accumulation of Gb3 in the pituitary gland (Fig. 5D, Supplemental Fig. 1) and adrenal gland (Fig. 5F) could support the latent endocrine dysfunctions in Fabry disease. Previous report confirming clear heterogeneous accumulation of Gb3 into the adrenal gland coincides with our findings of the accumulation of Gb3 in the endocrine system [7]. However, we could not confirm any evident endocrine dysfunction in this particular patient.

Ethical consideration

This study conformed to the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the Ethics Committee of The Jikei University School of Medicine.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2020.100623.

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