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【 CASE REPORT 】

Dapagliflozin for the treatment of collagenofibrotic glomerulopathy

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Abstract:
Collagenofibrotic glomerulopathy is a rare, incurable kidney disease characterized by severe proteinuria and extensive type III collagen deposition in mesangial and subendothelial spaces. To date, no effective treatment has yet been reported. A 45-year-old Japanese woman was treated daily with 10 mg dapagliflozin. Her eGFR slope improved from -3.61 mL/min/1.73 m^2/year over 4 years before treatment to 0.11 mL/min/1.73 m^2/year after 3 years of treatment. Additionally, her nephrotic-range proteinuria, initially exceeding 4 g/gCr, decreased to <2 g/gCr after dapagliflozin treatment. To our knowledge, this is the first documented case of effective treatment for collagenofibrotic glomerulopathy.

Key words: Collagenofibrotic Glomerulopathy, SGLT2 inhibitor, Dapagliflozin

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Introduction

Collagenofibrotic glomerulopathy (CG) is a rare kidney disease with approximately 100 reported cases worldwide (1). Of the 33,137 renal biopsy cases in the Johns Hopkins University archives, only two (one being a probable case) were biopsy-proven CG cases. Similarly, in the Japan Renal Biopsy Registry, just four cases of CG were found among 60,401 cases from 2007 to 2022 (2). Comprehensive reviews of the clinicopathological aspects of CG are available (1, 3). The disease is characterized by substantial deposition of type III collagen fibers in the mesangial area and subendothelial spaces and was first reported by Masaaki Arakawa in 1979 (4). CG has been reported in the literature under various names including primary glomerular fibrosis (5), collagen type III glomerulopathy (6), and collagenofibrotic glomerulonephropathy (7). In 1995, the World Health Organization added CG to its list of glomerulopathies with organized deposits (8).

CG typically manifests as a sporadic form in Japanese adults but has also been reported as an autosomal recessive systemic disorder in children (3). Patients often present with nephrotic-range proteinuria, hypertension, and progressive decline in renal function, frequently progressing to end-stage kidney disease (1, 3). To date, no specific treatment has yet been established.

Case Report

A 47-year-old Japanese woman with leg edema and hypertension visited the Nakayamadera Imai Clinic after recurrent episodes of edema over the previous 10 months. Upon presentation, she exhibited nephrotic-range proteinuria (4.2 g/gCr) and low serum albumin (3.1 g/dL). Her serum creatinine level was 0.91 mg/dL, with an estimated glomerular filtration rate (eGFR) of 53.0 mL/min/1.73 m^2, and she had high blood pressure at 160/100 mmHg. To confirm the diagnosis, she underwent a renal biopsy at the Kansai Rosai Hospital. The biopsy specimen contained 71 glomeruli, all

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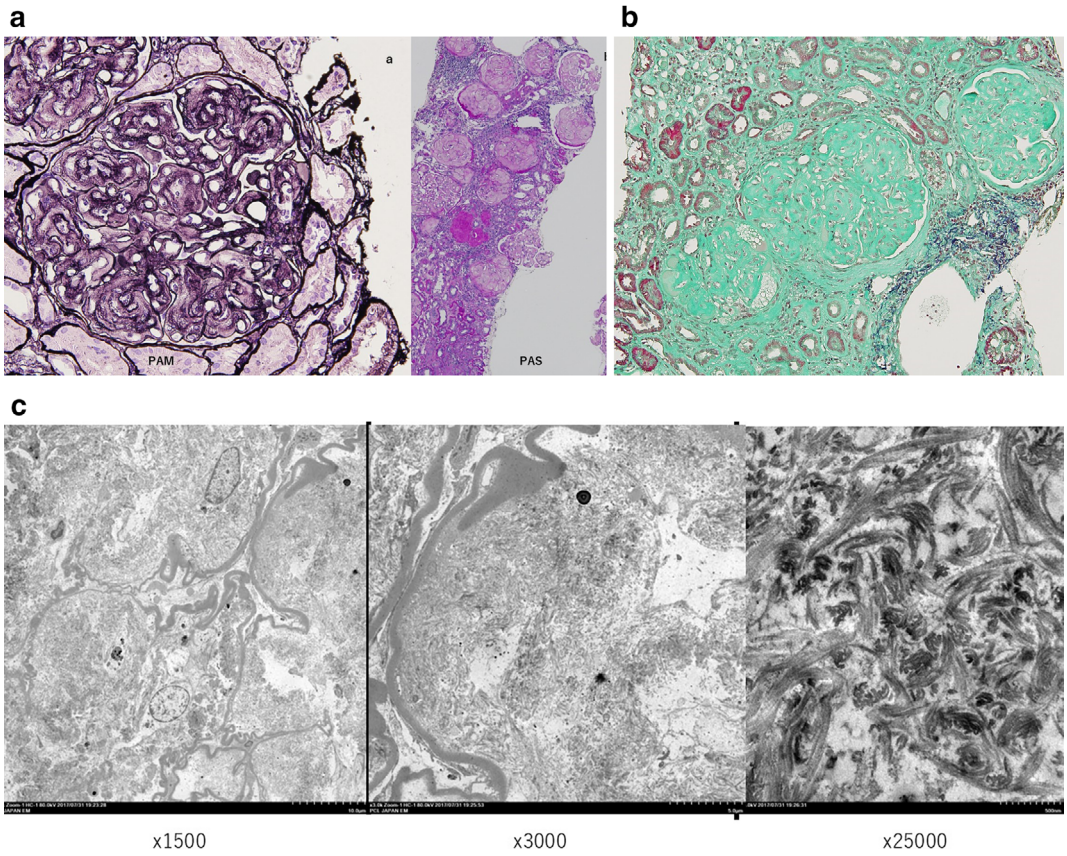

Figure 1. **a: The thickened areas show homogeneous, weak staining with Periodic acid-Schiff (PAS) stain (right). Double contours of the glomerular basement membrane are visible with Periodic acid-methenamine silver (PAM) stain (left). b: Mesangial expansion and double contours in the peripheral loop are highlighted with Elastica-Masson staining. c: Electron microscopy reveals markedly expanded extracellular spaces in the mesangium and subendothelial regions of the glomerular basement membrane (left) (original magnification ×1,500). The fibers appear curved and frayed in structure (right) (original magnification ×25,000).**

of which appeared enlarged with a distinct lobular structure, as shown in Fig. 1a. Light microscopy revealed narrowed capillary lumens owing to mesangial expansion and thickened capillary walls. The thickened areas showed homogeneous, weak staining with periodic acid-Schiff (PAS) stain, and double contours of the glomerular basement membrane were observed with periodic acid methenamine silver (PAM) staining (Fig. 21b). There was no evidence of either mesangial or endothelial cell proliferation.

An electron microscopic (EM) examination conducted at Kobe University Hospital revealed a marked accumulation of fibrillar materials, often curved or frayed, in the extracellular space of the mesangium and the subendothelial region of the glomerular basement membrane (Fig. 1c). Her serum procollagen type III peptide level was elevated at 3.9 U/mL, while her serum hyaluronan level had increased to 967 ng/mL by the sixth month.

To manage her condition, we treated her hypertension with amlodipine, olmesartan, eplerenone, and indapamide to reduce blood pressure and proteinuria (Fig. 2). Her systolic blood pressure stabilized between 120-130 mmHg, but proteinuria remained in the nephrotic range, exceeding 4 g/day over the next four years. Her renal function gradually declined, with an eGFR slope of -3.61 mL/min/1.73 m^2/year prior to initiating dapagliflozin. The eGFR slope was determined using the long-term eGFR plot (LTEP) method (9). In 2021, dapagliflozin was approved for clinical use in treating chronic kidney disease (CKD) in Japan, and at month 50, dapagliflozin was added to her antihypertensive regimen. Four months after starting dapagliflozin, proteinuria decreased to <2 g/day. Additionally, her eGFR slope improved to 0.11 mL/min/1.73 m^2/year, reflecting an improvement of 3.72 mL/min/1.73 m^2/year in her eGFR. This improvement in her renal function and a reduction in proteinuria were sustained over the following three years. By month 84, her serum procollagen type III peptide level had increased to 4.1 U/mL, and her serum hyaluronan level had increased to 2,157 ng/mL.

Discussion

This is the first report indicating that dapagliflozin improves both the eGFR slope and proteinuria in collagenofibrotic glomerulopathy (CG). CG is a rare, incurable kidney

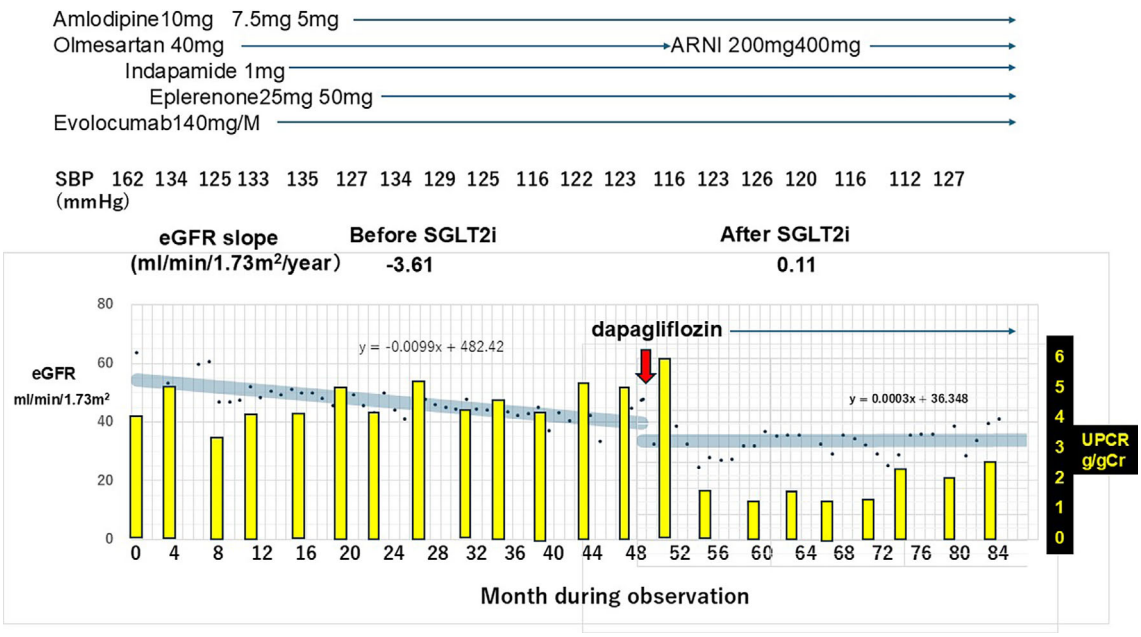

Figure 2. **Clinical course of collagenofibrotic glomerulopathy.**

disease characterized by nephrotic-range proteinuria, and it is frequently associated with hypertension. We managed the patient's high blood pressure with antihypertensives, including renin-angiotensin system inhibitors, aiming to maintain the blood pressure within the normal range of less than 130/80 mmHg. Despite this, the eGFR slope showed a persistent decline during antihypertensive treatment (-3.61 mL/min/1.73 m^2/year), and nephrotic-range proteinuria persisted for four years. Four years after starting antihypertensive treatment, we administered 10 mg of dapagliflozin in addition to the existing regimen. Following this, the eGFR slope improved (0.11 mL/min/1.73 m^2/year), and proteinuria decreased to less than half of the previous levels.

How did dapagliflozin improve the renal function and proteinuria in the CG? First, SGLT2 inhibitors such as dapagliflozin reduce glomerular blood pressure, which is associated with improvements in the renal function and proteinuria (10). In this case, a modest initial drop in eGFR was observed shortly after dapagliflozin administration. The eGFR initially measured 47.4 mL/min/1.73 m^2 but declined to 34.8 mL/min/1.73 m^2 one month after treatment began. Likewise, persistent severe proteinuria (8.3 g/gCr) was reduced to 4.0 g/gCr within a month. Second, dapagliflozin may exert direct effects on podocytes, thereby crucially maintaining the actin cytoskeleton architecture (11). SGLT2 is upregulated in podocytes in idiopathic membranous nephropathy with proteinuria. In a mouse model of protein-overload proteinuria, podocytes expressed SGLT2, which increased with an increasing protein load. Dapagliflozin reduced the protein/creatinine ratio by 63% and limited cytoskeletal changes induced by excessive albumin levels. Third, tubular damage in renal disease often determines kidney lifespan, as substantial proteinuria damages the proximal tubule through over-reabsorption of albumin. SGLT2 inhibitors protect renal tubular cells and podocytes by promoting ketone body-induced mTORC1 inhibition (12). Fourth, empagliflozin alleviated the high-fat diet (HFD)-induced increase in autophagic demand and prevented autophagic stagnation in the proximal tubules. In addition, empagliflozin decreased albumin exposure and autophagic demand in 5/6 nephrectomized mice. Autophagy improvement may therefore be critical for the renoprotection mediated by SGLT2 inhibition (13).

The pathogenesis of CG, particularly the deposition of type III collagen in the glomeruli, remains unclear. Serum procollagen type III peptide levels are notably high in the CG (5). It remains unclear whether the source of type III collagen is the mesangial cells of the kidney (14, 15) or other organs, such as the liver (16). In this case, serum procollagen type III peptide levels remained unchanged following SGLT2 inhibition, suggesting that the renal protection afforded by dapagliflozin was unrelated to type III collagen production in the CG.

In conclusion, we observed that dapagliflozin positively affected the clinical course of CG by improving the eGFR slope and reducing proteinuria, independent of any changes in the serum type III collagen levels.

Author's disclosure of potential Conflicts of Interest (COI).

Enyu Imai: Honoraria of lecture fee, AstraZeneca.

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