Two brothers with collagenofibrotic glomerulopathy

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Received: 19 November 2013 / Accepted: 31 August 2014 / Published online: 18 September 2014
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Abstract Collagenofibrotic glomerulopathy is a rare glomerular disease characterized by extensive accumulation of atypical type III collagen fibers within the mesangial matrix and subendothelial space. Laboratory evaluation of this disease shows a marked increase in serum procollagen III peptide (P III P) levels. Here, we report the case of two brothers with collagenofibrotic glomerulopathy confirmed by histology. Patient 1 presented with proteinuria and hypertension and patient 2 presented with nephrotic-range proteinuria. Immunohistochemistry revealed strong staining for antibodies to type III collagen in the widened subendothelial spaces in both patients. Electron microscopy revealed numerous collagenous fibers in the mesangium and subendothelial space. P III P levels were elevated in both patients. Most reported cases of collagenofibrotic glomerulopathy, including the adult-onset type, have been sporadic. Within the limits of our literature search, this is only the third report of adult siblings with collagenofibrotic glomerulopathy confirmed by histology. This report indicates that it may be beneficial to measure serum P III P levels in the siblings of patients diagnosed with adult-onset collagenofibrotic glomerulopathy.

Keywords Collagenofibrotic glomerulopathy · Collagen type III glomerulopathy · Type III collagen · Procollagen III peptide · Familial nephropathy

Introduction

Collagenofibrotic glomerulopathy was first reported in 1979 by Arakawa et al. [1] at the annual meeting of the Japanese Society of Nephrology. This is a rare glomerulopathy characterized by extensive accumulation of atypical type III collagen fibers within the mesangial matrix and subendothelial space. The cause and pathogenesis of the disease are entirely unknown. The most common clinical presentation is proteinuria with or without nephrotic syndrome. A diagnosis can be made when typical histological findings are proven by electron microscopy. To the best of our knowledge, 34 cases of collagenofibrotic glomerulopathy have been reported in the English language literature, as far as we could ascertain [2–19]. Although most cases were sporadic, there were a few reports of affected siblings [2, 3, 9–11], of which only two documented the condition in adult siblings [9, 11]. Here, we report a case, only the third such case as per our knowledge, of familial collagenofibrotic glomerulopathy that was confirmed by histological evidence in two adult siblings.

Case report

A 64-year-old man (patient 1) with a 15-year history of hypertension was admitted to Anjo Kosei Hospital for the evaluation of proteinuria in 2011. Hypertension and proteinuria were first detected during an annual medical checkup 15 years back; however, he did not undergo a

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detailed examination at that time. He was referred to our hospital because of persistent proteinuria 2 years back. The degree of proteinuria had gradually increased from 1+ to 3+ over the past 2 years; however, renal function had remained stable, and he did not show evidence of edema or any other symptoms then. On admission, his blood pressure was 154/78 mmHg. Physical examination revealed no abnormalities such as bone or nail dysplasia. Urinalysis revealed moderate proteinuria (2–3 g/day) with no pathological sediments. Bence-Jones protein was not detected in the urine. His hemoglobin level was 12.0 g/dL, hematocrit 36.9 %, and WBC count 7000 cells/ μ L with normal differentiation. Serum levels of total protein, albumin, creatinine, blood urea nitrogen, and uric acid were 6.6 g/dL, 4.1 g/dL, 0.81 mg/dL, 22 mg/dL, and 6.4 mg/dL, respectively, while those of electrolytes, blood glucose, and HbA1c were within normal limits. The serum protein electrophoretic pattern showed no monoclonal peak. Serum immunoglobulin (IgG, IgM, IgA, C3, C4, and CH50 levels were all within normal limits. Neither antinuclear antibody nor rheumatoid factor was detected. Serum procollagen III peptide (P III P) levels as measured by an immunoradiometric assay (P III P RIA-gnost c.t.kit, Behringwerke Co., Marburg, Germany) were elevated to 2.6 U/mL (normal range 0.3–0.8 U/mL). Percutaneous kidney biopsy was performed in 2011. He was prescribed imidapril 10 mg/day and amlodipine 5 mg/day and followed on an outpatient basis. His renal function has been stable for 2 years since hospitalization.

The older brother of patient 1, a 67-year-old man (patient 2), was referred to Ikeda City Hospital for evaluation of the prolonged proteinuria and renal dysfunction in 2006. His proteinuria was detected by routine physical examination 10 years back. His laboratory findings were as follows: 24-h urinary protein 6.3 g; hemoglobin 12.3 g/dL; serum total protein 4.8 g/dL; albumin 2.7 g/dL; creatinine 1.54 mg/dL; blood urea nitrogen 23 mg/dL; and uric acid 7.2 mg/dL. Serum electrolytes, blood glucose, and HbA1c levels were within normal limits. Serum IgG, IgA, IgM, and CH50 levels were all within normal limits, while serum P III P levels were elevated to 4.9 U/mL. The antinuclear antibody titer was 1280, although the reason for this increase was uncertain. Rheumatoid factor was not detected. A kidney biopsy was performed in 2006. Despite conventional treatment without glucocorticoid or immunosuppressive agents, his renal function deteriorated to end-stage renal failure, necessitating the initiation of hemodialysis therapy in 2010. The eldest brother of these two patients refused to visit a clinic and died of renal failure. Their parents were not consanguineous.

Fig. 1 Light microscopy with periodic acid–Schiff staining; $\times 400$. The images show a glomerulus with thick capillary walls and subendothelial accumulation of pale staining homogeneous material, which is also observed throughout the mesangial regions (patient 1)

Kidney biopsy findings

The kidney specimen of patient 1 contained 52 glomeruli, none of which showed global sclerosis. Glomerular cells are decreased because of too much deposits. Glomerular tufts (capillary lumen) are narrowed and the number of capillary lumens severely decreased (Fig. 1). The mesangium is expanded with eosinophilic material that occupied the capillary lumens. This material stained weakly with periodic acid–Schiff stain, similar to amyloid substance; whereas, Congo red and thioflavin T staining were completely negative. The basement membrane showed a double-contour appearance with periodic acid methenamine silver (Fig. 2a). A few renal tubules were atrophic, and lymphocytic infiltration was observed in a small area.

Immunofluorescence revealed focal mesangial deposits of IgM and C3 in a nonspecific fashion. No significant fluorescence for IgG, IgA, C4, or fibrinogen was observed. Staining for antibodies to type III collagen was observed in capillary lumen or GBM, probably because of much collagen III deposition near or within the basement membrane (Fig. 3).

Electron microscopy using tannic acid staining showed fibrous materials in the mesangial and subendothelial spaces. These fibrils were curved, frayed, and serpentine and formed irregularly arranged bundles in longitudinal sections. The fibers exhibited a transverse band structure with distinctive periodicity, similar to type III collagen fibers (Fig. 4).

Fig. 2 A double-contour appearance with periodic acid methenamine silver; $\times 400$ (**a** patient 1; **b** patient 2)

The kidney specimen of patient 2 contained 33 glomeruli, 3 of which showed global sclerosis. The histological findings of the glomeruli were essentially the same as those observed in the specimen from patient 1 (Fig. 2b). A moderate degree of interstitial fibrosis and arteriolar hyalinosis was observed. Immunofluorescence showed staining of type III collagen in the subendothelial spaces, while electron microscopy showed fibrous materials in the enlarged subendothelial spaces.

Discussion

Collagenofibrotic glomerulopathy was previously documented mainly in Japan, but of late, reports from Europe [4], South America [6], North America [7], and other countries in Asia are emerging [8, 9, 20]. Although it is mostly sporadic, 17 cases from 8 families were those of siblings born to parents without renal disease [2, 3, 9–11]. Table 1 summarizes previous reports on the familial

Fig. 3 Immunohistochemical staining; $\times 400$. Positive staining in the mesangium and subendothelial space using antibodies to type III collagen (patient 1)

Fig. 4 Electron microscopy using tannic acid staining; $\times 10000$ (patient 1), marked accumulation of fibrillar substances in the mesangial area and subendothelial space. Characteristic periodicity of collagen fibers is observed

occurrence of collagenofibrotic glomerulopathy, including suspected cases. An autosomal recessive pattern of inheritance was suggested on the basis of the observations of Salcedo [2] and Gubler et al. [3]. Other reports have speculated on the presence of a child-onset type and an

Table 1 Summary of previous reports on the familial occurrence of collagenofibrotic glomerulopathy

References	Family	Case	Age (year)	Sex	Kidney biopsy	Serum P III P	Parents
Salcedo [2]	1	1	9	M	+	ND	Con
		2	2	F	–	ND	
		3	3	M	–	ND	
Gubler [3]	2	4	<1	M	+	ND	ND
		5	2	F	+	ND	
	3	6	1	M	+	ND	Con
		7	1	F	+	ND	
		8	5	F	+	ND	ND
	5	9	6	M	+	ND	
		10	15	M	+	ND	ND
Mizuri [14]	6	11	3	M	+	ND	
		12	53	F	+	Elevated	ND
Tamura [15]	7	13	ND	M	–	ND	
		14	25	F	+	Elevated	Not Con
		15	33	F	+	Elevated	
Chen [13]	8	16	31	M	+	Elevated	Con
		17	32	M	+	Elevated	
Current cases	9	18	63	M	+	Elevated	Not Con
		19	68	M	+	Elevated	

ND not described, Con consanguineous

adult-onset type [5, 20, 21]; none of the adult-onset cases in these reports had a familial occurrence. However, in addition to the reports of Tamura et al. [11] and Chen et al. [9], this is the third report of adult siblings with collagenofibrotic glomerulopathy confirmed by histological findings. We therefore consider that some cases of the adult siblings may be born to patients who carry an autosomal recessive mutation. However, it is difficult to identify a familial occurrence because genetic diagnosis of the disease has not established.

The clinical manifestations of collagenofibrotic glomerulopathy include proteinuria, hypertension, anemia, and edema of the lower extremities. In the majority of cases, the cause of admission is edema of the lower extremities or persistent proteinuria. Proteinuria may reach the nephrotic range in approximately 50–60 % patients [21, 22]; this finding was also observed in our patient 2. Previous reports have indicated that collagenofibrotic glomerulopathy is slowly progressive [4, 5]. Suzuki et al. [23] reported that 7 of 14 patients progressed to end-stage renal disease within 7–10 years after the appearance of proteinuria. They conducted a questionnaire survey in 2004 in Japan and demonstrated a 10-year renal survival rate of 49 % after diagnosis.

Histologically, the glomeruli of patients with collagenofibrotic glomerulopathy show lobular accentuation with mesangial and subendothelial deposits of pale homogenous fibers that are weakly positive on periodic acid–Schiff staining, fuchsinophilic on Masson trichrome

staining, and negative for Congo red staining. The glomerular basement membrane is not thickened and does not contain collagen fibers, as observed in patients with nail–patella syndrome. The fibers are not straight and tend to curve or fray, forming irregularly arranged bundles. These fibers are visualized more readily using tannic acid, lead, or phosphotungstic acid staining.

Increased serum P III P levels are found in patients with collagenofibrotic glomerulopathy who present with fibrosis, indicating excessive conversion of type III procollagen to type III collagen [20]. Median serum P III P levels in patients with chronic kidney disease have been reported to be twice that in healthy subjects [13], whereas the levels in patients with collagenofibrotic glomerulopathy are 10–100 times that in healthy subjects [22]. Ozu et al. [14] proposed that the increase in serum P III P levels correlates with the decrease in creatinine clearance. With regard to the etiology of collagenofibrotic glomerulopathy, elevated serum P III P levels suggest that this disorder is related to overproduction or abnormal metabolism of type III collagen [3, 10, 15].

A definitive therapy for this disorder has not yet been established. Supportive therapy by control of hypertension and edema may help to relieve the symptoms. Systemic glucocorticoid therapy (prednisolone, 40 mg/day) appears to be effective for treating renal dysfunction, anemia, and proteinuria temporarily and for decreasing serum P III P levels [5]. Yoshida et al. [12] suggested that dipyridamole may also be effective. Furthermore, Suzuki et al. [23]

reported a case of renal transplantation in a patient with collagenofibrotic glomerulopathy. The postoperative course of this patient was uneventful, with good renal function being maintained by immunosuppressive therapy.

In conclusion, we reported a case of familial adult-onset collagenofibrotic glomerulopathy in two brothers. Serum P III P levels were elevated in both patients. This report indicates that it may be beneficial to measure serum P III P levels in the siblings of patients diagnosed with adult-onset collagenofibrotic glomerulopathy.

Acknowledgments This case report received an excellent presentation award at the 42nd Japanese Society of Nephrology Western regional meeting. We thank Norihiko Suzuki, Naoko Asano, Yuriko Sawa, Naoto Kishikawa, Masaru Kawai, Hideyo Mukai, and Yoshiko Koiso for excellent technical assistance. The authors would like to thank Enago (<http://www.enago.jp>) for the English language review.

Conflict of interest All the authors have declared no competing interests to declare.

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