Nephrotic Syndrome with Massive Accumulation of Type I and Type III Collagen in the Glomeruli

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A 54-year-old woman with nephrotic syndrome underwent renal biopsy. By light microscopy, the glomerular capillary lumen was remarkably narrowed because of diffuse accumulation of Periodic acid Schiff (PAS) positive material along the glomerular capillary wall. By electron microscopy, collagenous fibers were observed in the mesangium and subendothelial area. The fibrous material reacted with antibodies against type I and III collagen but not with those against laminin or type IV collagen by an indirect immunofluorescence technique. This case seemed to be a case of collagenofibrotic glomerulonephropathy.

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Key words: human, glomerulus, collagenous fibers, subendothelial expansion

Introduction

Collagenous material is seen in the glomerular lesion in some renal diseases such as renal amyloidosis (1), multiple myeloma (2), diabetic nephropathy (3), and light chain disease (4). Nail-Patella syndrome (NPS) shows characteristic alterations of the glomerular basement membrane (GBM) with the increase of collagen fibrils and lucent lesions (“moth-eaten” appearance) in the GBM (5, 6). Alpers et al (7) reported seven cases with glomerular disease that had a characteristic ultrastructural appearance of amyloid-like deposits. Similar cases are reported by Duffy et al (8) and Sturgill et al (9) as non-amyloidotic fibrillary glomerulonephritis.

In this paper, we report a case with a unique glomerular lesion with massive accumulation of collagen fibers in the subendothelial space and mesangial area, which manifested clinically as nephrotic syndrome. Recently, several Japanese cases in which the renal pathology was similar to that of the present case have been summarized by Arakawa and Yamanaka (10); they proposed it to be a glomerular disease of a new entity. We examined the lesion histologically and immunohistochemically to identify these fibers and we describe the 4-year follow-up.

Case Report

A 54-year-old Japanese woman was detected to have proteinuria six years previously. She had suffered from hypertension for ten years at that time. Antihypertensive agents were administered but the systolic blood pressure remained over 150 mmHg. Moderate proteinuria continued but she did not feel edema nor other symptoms. She was admitted to Nagoya University Hospital on December 12, 1988, when she noticed leg edema. The patient had been working in a department store and had no history of alcoholism, exposure to chemicals, or drug abuse. There was no family history of renal disease or systemic diseases. Her blood pressure on admission was 180/92 mmHg. Physical findings disclosed moderate pretibial leg edema but no other abnormalities including the dysplasia of bone and nail were found.

Laboratory findings were as follows: Urinalysis revealed moderate proteinuria (3–5 g/day) with pathological sediments. Bence-Jones protein was not detected in the urine. The hematocrit was 35.5%, hemoglobin 7.57 mmol/l, with normal differentials. Serum total protein was 56 mg/l, albumin 464 μmol/l, creatinine 70.7 μmol/l, urea 7.85 mmol/l and uric acid 512 μmol/l. Serum electrolytes were within the normal limits. Blood glucose and Hb-A1 levels were normal. The protein...
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Electrophoretic pattern of the serum showed no monoclonal peak. Serum immunoglobulin G (IgG) was decreased, but IgM, IgA, C3, C4 and CH50 were within the normal range. Auto-antibodies were not detected. Chest and abdominal X-rays were normal and an excretory urographic examination, including nephrotomograms, revealed that the kidneys were normal in size and shape. She was followed up at the out-patient clinic. Percutaneous renal biopsy was performed at Masuko Memorial Hospital in January 1990.

Renal tissue was processed for light (LM), immunofluorescent (IF) and electron microscopic examination. The specimens for LM contained 18 glomeruli. One glomerulus showed global obsolescence. In other glomeruli, glomerular tufts were apparently narrowed because of diffuse accumulation of weakly PAS positive material in the luminal side of the capillary walls (Fig. 1a). Extra-capillary or intra-capillary cell proliferation was not prominent and there was only slight infiltration of inflammatory cells. The increased material was strongly positive with aniline blue staining (Fig. 1b) and was

Fig. 1. Light micrographs of the glomerulus showing diffuse accumulation of homogeneous material along the capillary wall and in the mesangium, which is weakly positive with PAS staining (a, ×400) and strongly positive with aniline blue in Mallory-azan staining (b, ×400).

Fig. 2. An electron micrograph of a glomerulus. Note narrowed capillary lumen. Epithelial foot processes are flattened and epithelial cells were detached in some parts (inset) (×2,600, inset ×1,000).
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weakly stained with Periodic acid-methenamine-silver (PAM). The tissue was negative under polarized light microscopy after staining with Congo red. In some part of the capillary walls, “double contours” were found with PAM staining. The renal tubules were focally atrophic and the infiltration of lymphocytes was observed in some parts. Arterioles showed moderate thickening of the walls and there was intimal and medial hypertrophy in the interlobular arteries.

By electron microscopy, fibrous materials were observed in the mesangial and subendothelial areas, which led to the irregular expansion of subendothelial space and mesangial matrix (Fig. 2). However such fibers were not seen in the lamina densa or lamina rara externa of the GBM. There was no electron lucent lesion on the lamina densa, which is the characteristic feature of NPS. There were no electron dense deposits in the mesangium or in the capillary walls which are typical of mesangioproliferative glomerulonephritis and other types of primary glomerulonephritis. Epithelial cells were degenerated and detached in some parts (Fig. 2, inset). On high power field, some parts of the lesions contained of amorphous plasma-like substances with edematous subendothelial expansion. The increased fibers were irregularly curved and formed bundles by themselves (Fig. 3). There was no abnormal fibrous structure in the interstitium.

IF revealed positive IgM and Clq staining in the partially linear pattern along glomerular capillary walls, but no significant staining for IgG, IgA, C3, C4, Fib, or light chains (kappa and lambda) was observed. In order to clarify the nature of the fibrous lesions, we stained the frozen sections by indirect IF technique with rabbit anti-murine laminin and anti-human type IV collagen antibodies (Advance Biofactures Corp., New York). The sections were also stained with mouse monoclonal anti-type I (11) and anti-type III collagen antibodies (12, 13). The antibodies against laminin and type IV collagen reacted with capillary walls as well as with Bowman's capsule and tubular basement membrane, but not with the fibrous material (Fig. 4a and 4b). In contrast, antibodies against type I and type III collagen reacted strongly with the material which showed homogeneously eosinophilic staining in the glomerular capillary walls or in the mesangium when observed by LM (Fig. 4c and 4d).

At present, the nephrotic state of this patient has slightly progressed. Urinary protein excretion (24-hour) is more than 5 g/day and serum total protein is 48 g/l and albumin 333 µmol/l. The serum level of procollagen III peptides is constantly higher than 4,000 U/l (normal range 300–800 U/l). The renal function is slightly impaired at present compared with that of her first admission to our hospital. Blood pressure is controlled at 140/90 mmHg by nifedipine (30 mg/day) and enalapril (5 mg/day). Treatment with dipyridamole (300 mg/day) was not effective for improving the proteinuria. The whole clinical course is shown in Table 1.

Fig. 3. An electron micrograph showing the granular proteinaceous and fibrous material in the subendothelial space. The increased fibers are composed of thick fibers with a lucent area (arrowheads) and thinner electron dense fibrils (arrows) (×5,000).
Fig. 4. Indirect immunofluorescence staining for laminin (a: \(\times 200\), inset \(\times 1,000\)), type IV collagen (b: \(\times 400\), inset \(\times 1,000\)), type I collagen (c: \(\times 200\)) and type III collagen (d: \(\times 200\), inset \(\times 1,000\)). Laminin and type IV collagen are present in the duplicated glomerular basement membranes as well as in Bowman’s capsule and in the tubular basement membrane but not in the material accumulated in the subendothelial area. However, both type I and III collagen are detected in the mesangium and along the capillary walls where the PAS-positive material is observed in light microscopy.

Discussion

The glomerular lesion of this patient is characterized by the diffuse accumulation of the fibrous material, which is strongly anilin-blue positive and weakly PAS and PAM positive, in the subendothelial and mesangial areas. The narrowing of the glomerular capillary lumen and the double contoured capillary walls seem to be due to the diffuse deposition of this fibrous material. However, cell proliferation is not prominent in either the intracapillary or extracapillary sites. This material seems to consist of types I and III collagen based on the results of IF and EM findings. Amyloid fibrils were not present because of the absence of reaction with Congo red, anti-light chain (kappa or lambda chain) antibodies or characteristic amyloid fibrils. From these data, the massive deposition of collagen fibers in glomeruli was considered to be different from amyloidotic nephropathy, light chain diseases and non-amyloidotic fibrillary glomerulonephritis. It is well known that NPS shows the presence of collagen fibrils and electron lucent areas (“moth-eaten” appearance) within lamina densa of GBM (5, 6), which are the pathognomonic lesions of NPS (6, 14, 15). But the present case has no abnormality in her nail or skeletal systems, and there was no accumulation of collagen fibers in the lamina densa and lamina rara externa of the GBM.

As far as we know, there are some reports of similar glomerular lesions in Japanese (16–18) and there are two case reports from other countries (19, 20). Arakawa and Yamanaka (10) have summarized the Japanese cases and proposed a new entity of a glomerular disease, called collagenofibrotic glomerulonephropathy. In these cases, the age of onset varied between 6 and 70s’ and there was no difference in incidence between males and females. Ikeda et al (21) reported a similar glomerular lesion and they suggested that the nephropathy is caused by a primary increase in atypical type III collagen fibers in the glomeruli with the increase of the serum level of procollagen III (P-III-P). Imbasciati et al concluded that the accumulated collagen was consisted of types I and III (20). In the present case, the fibrous material in the glomerulus consisted of type I as well as type III collagen but not of laminin or type IV collagen which was observed.
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Table 1. Clinical Course.

<table>
<thead>
<tr>
<th>Year</th>
<th>'89</th>
<th>'90</th>
<th>'91</th>
<th>'92</th>
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<tbody>
<tr>
<td>Therapy</td>
<td>Nifedipine 30mg/d.</td>
<td>Pindolol 15mg/d.</td>
<td>Enalapril 5mg/d.</td>
<td>Dipyridamole 300mg/d.</td>
</tr>
<tr>
<td>Edema</td>
<td>+ + + ± + + # # + + + + + æf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (g/24hr.)</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T.P. (g/l)</td>
<td>alb. 600</td>
<td>400</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>0</td>
<td>150</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>serum PIII-P level (U/l)</td>
<td>4,000 ††</td>
<td>5,300 ††</td>
<td></td>
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</tr>
</tbody>
</table>

▼ : Renal Biopsy  * PIII-P : procollagen III peptide (normal: 300~800U/l)

in both sides of the GBM with the increase in the serum level of P-III-P. The pathogenesis of the disease is unknown, but the overproduction of type III collagen in the mesangial cell has been speculated by Arakawa and Yamanaka (10) and Imbasciati et al (20).

The common features of these cases are the massive proteinuria. The pathogenesis of the proteinuria is not known, but the degeneration and detachment of the epithelial cells from GBM were observed in places in our case. There are little mentions about the epithelium in other reports. But it may be possible that the endothelial injury due to the massive accumulation of fibers in the subendothelial space leads to the secondary damage to the epithelium, or detachment of the epithelium was caused partially because of the adhesion defects by abnormal collagen synthesis, which might induce the massive proteinuria. Epithelial cells have an important role in regulating permeability of the GBM (22). Messina et al (23) and Whiteside et al (24) reported that the glomerular epithelial detachment occurred coincidentally with the development of massive proteinuria in puromycin-aminonucleoside nephrosis in rats. We speculate that the detachment of the epithelial cells plays an important role in the mechanism of proteinuria.

Clinically, there is little mention about the treatment and no long-term observation was found in the previous reports. We used anti-hypertensive drugs (nifedipine and enalapril) and dipyridamol and observed the patient for about four years. The effects of the medicine are unclear but the renal function has been maintained with only a slight elevation of the serum creatinine level (115 µmol/l) for 4 years after the onset of the nephrotic syndrome (Table 1).

In conclusion, we reported a nephrotic patient with a rare glomerular lesion of abundant collagen deposition in the subendothelial space and mesangial area. This case seemed to be comparable to the glomerular disease, “collagenofibrotic glomerulonephropathy”, which was recently proposed by Arakawa and Yamanaka (10). The pathogenesis and clinical course of this case are unclear at present, but accumulation of similar cases may help to elucidate this peculiar glomerular lesion.

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