Obesity-Related Nephropathy Associated with a History of IgA Nephropathy

Nobuo Tsuboi, Tetsuya Kawamura, Takeo Ishii and Tatsuo Hosoya

Abstract

This report describes the case of a 57-year-old man who underwent a repeated renal biopsy 25 years after the first biopsy in which the diagnosis of IgA nephropathy was made. Although the patient exhibited gradually increasing proteinuria and a slowly progressive renal impairment, the histological findings of the repeat biopsy revealed no evidence of either glomerular inflammatory changes or IgA deposition. Instead, a marked decrease in the glomerular density and hypertrophy of the remnant glomeruli were noted. Almost a complete disappearance of urinary protein excretion by a calorie-restricted diet indicated that the patient’s obesity and its related factors may have contributed to the present nephropathic development.

Key words: IgA nephropathy, proteinuria, obesity, hyperfiltration

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Introduction

Obesity-related nephropathy has recently been proposed to be a cause of renal injury (1, 2). The pathological characteristics of obesity-related nephropathy are glomerulomegaly and focal segmental glomerulosclerosis (FSGS) (1). The clinical manifestation of obesity-related FSGS differs from the classic idiopathic FSGS and it is characterized by less proteinuria and a more indolent progression (1). Although the precise mechanisms of this abnormality are currently unknown, studies have indicated that, in obese patients, renal hyperperfusion and hyperfiltration are markedly increased (3, 4). Since obesity induces single-nephron adaptations even at normal nephron capacity, nephron overwork and the risk of intraglomerular hypertension in obesity would thus be exaggerated if the total number of nephrons was already low. This hypothesis is supported by a recent study showing that obese patients are at high risk of developing proteinuria and renal impairment when a unilateral nephrectomy is performed (5). However, the notion that excess weight accelerates the progression of renal impairment associated with a low nephron number should not be restricted to surgical causes of nephron loss. Of perhaps greater clinical importance, similar additive deleterious effects of obesity would therefore be expected in individuals with chronic kidney diseases which could potentially cause a progressive nephron loss.

Case Report

The patient was a 57-year-old man airplane pilot with a medical history of a tonsillectomy at 10 years of age. In March 1980, when he was 31 years old, he developed macroscopic hematuria after experiencing symptoms of an upper respiratory infection and was admitted to the hospital. At that time, his serum creatinine concentration (s-Cr) and 24-hour creatinine clearance (Ccr) were 0.7 mg/dL and 130 mL/min, respectively. The serum levels of streptococcal antigen did not increase. A renal biopsy showed diffuse cellular proliferation around the mesangium area and cellular crescents in more than 20% of the glomeruli (Fig. 1A and Table 1). Observations by electron microscopy showed the mesangium and para-mesangium areas contained electron-dense deposits (Fig. 1C), and immunofluorescence was positive for immunoglobulin A (IgA) in the corresponding locus. The histological diagnosis of the first-time biopsy was IgA nephropathy (IgAN). After being administered antiplatelet drugs for about four months, his urine protein excretion decreased to 0.1 g/24 hours. The patient requested termination of the...
medication before being discharged after his first admission to the hospital. Therefore, we performed a follow-up (second) renal biopsy after informed consent to confirm the presence of histological improvement (Table 2).

Figure 2 shows the clinical course of 25 years from the time of disease onset. After the patient was discharged from the hospital for the first time, low degrees of proteinuria and microscopic hematuria were occasionally observed for about 10 years. However, his urine protein excretion gradually increased, and constantly exceeded 1.0 g/24 hours at 45 years of age, and it reached 2-3 g/24 hours at 56 years of age. He gradually became obese as he grew older, and his body weight, which was around 60 kg level at first admission, increased to more than 80 kg in recent years. His S-Cr concentration increased to 1.2 mg/dL and the 24-hour Ccr decreased to 70-80 mL/min. No medication has been prescribed for about 25 years since his first discharge from hospital by request of the patient. A repeat (third) renal biopsy was taken due to signs of progressive renal impairment.

Upon admission, his body weight was 84 kg (body mass
Table 1. Clinical and Laboratory Findings at the First and Second Admissions

<table>
<thead>
<tr>
<th></th>
<th>1st admission</th>
<th>2nd admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31</td>
<td>57</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>20.0</td>
<td>28.4</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>100/54</td>
<td>130/90</td>
</tr>
<tr>
<td>Urinary protein excretion (g/24hrs)</td>
<td>1.1</td>
<td>1.98</td>
</tr>
<tr>
<td>Urinary red blood cell sediments (high power field)</td>
<td>Many</td>
<td>1~4</td>
</tr>
<tr>
<td>24hr-creatinine clearance (mL/min)</td>
<td>130</td>
<td>80</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dL)</td>
<td>171</td>
<td>214</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>5.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>-</td>
<td>114</td>
</tr>
<tr>
<td>Serum Immunoglobulin A (mg/dL)</td>
<td>444</td>
<td>232</td>
</tr>
</tbody>
</table>

Figure 2. The clinical course of 25 years from the onset. The patient gradually became obese as he grew older, and his body weight (BW), which was around 60 kg at first admission, increased to more than 80 kg in recent years. In parallel, the patient’s urine protein excretion (UPE) gradually increased, and constantly exceeded 1.0 g/24 hours at 45 years of age, and it reached 2-3 g/24 hours at 56 years of age. The 24-hour creatinine clearance (Ccr), which was 130 mL/min at the time of first hospitalization, decreased to 70-80 mL/min.

index, BMI 28.4 kg/m^2) and his abdominal circumference was 94 cm, thus indicating a tendency towards adiposis. His blood pressure was 130/98 mmHg. The laboratory findings on admission were as follows: blood urea nitrogen 15 mg/dL (normal range 8-20 mg/dL), s-Cr 1.2 mg/dL (normal range 0.5-1.1 mg/dL), serum total protein 7.3 g/dL (normal range 6.7-8.3 g/dL), serum albumin 4.5 g/dL (normal range 3.5-5.2 g/dL), total cholesterol 214 mg/dL (normal range 120-219 mg/dL), high density lipoprotein-cholesterol (HDL-C) 43 mg/dL (normal range >40 mg/dL), triglyceride 143 mg/dL (normal range 30-149 mg/dL), fasting blood sugar (FBS) 114 mg/dL (normal range 65-109 mg/dL) and HbA1c 5.2% (normal range 4.3-5.8%). The levels of serum immunoglobulins and complement factors were all within the normal range. All other serology findings, including anti-nuclear antibody, hepatitis B surface antigen, hepatitis C antibody, antistreptolysin O antibody, serum cryoglobulin, anti-neutrophil cytoplasmic antibody, and anti-glomerular basement membrane antibody were negative or normal. There was no M-spike on serum protein electrophoresis. A urinaly-
Clinical course of the follow-up. After discharge, the patient’s body weight steadily decreased. Eleven months later, his body weight and abdominal circumference were 73 kg (-13.1%) and 85 cm (-9.6%), respectively. In parallel, his blood pressure had decreased to a level of optimal control. The plasma insulin concentration decreased markedly from two months onward. The urinary protein excretion levels (UPE) decreased markedly to below 0.3 g/24 hours from seven months onward.

Sis showed negative glucose, (3+) protein, 1-4 white blood cell count/hpf and 1-4 red blood cell count/hpf. Neither granular cast nor red blood cell cast was detected. The 24-hour Ccr was 80 mL/min. Urinary protein excretion was 1.98 g/24 hours. The kidneys were determined to be normal in size on ultrasound. The clinical and laboratory findings at the first and second admissions are summarized in Table 1.

The renal biopsy contained 18 glomeruli for light microscopic observation, 6 of which were globally sclerotic. No FSGS lesion was found. The glomeruli appeared markedly enlarged without hypercellularity and no crescents were seen (Fig. 1B, Table 2). Neither thickness nor irregularity was observed in the glomerular basement membrane. Approximately 30% of the cortex had patchy interstitial expansion due to mild inflammatory infiltrates of mononuclear cells and fibrosis. The area of the interstitial lesion was not restricted to any particular vascular territory. Regarding the vascular system, moderate arteriolar hyaline degeneration was observed in the small arteries (Fig. 1D). Two glomeruli were analyzed by immunofluorescence and showed only trace staining for immunoglobulin M (IgM) in the mesangial area and peripheral capillary wall. Staining for immunoglobulin G (IgG), IgA, C3, and C1q were negative. On ultrastructural evaluations, the glomeruli were devoid of any electron-dense deposits, significant foot process effacement, or the detachment and/or hypertrophy of podocytes.

Since the renal biopsy findings showed no evidence of a recurrence of acute inflammation, immunosuppressive medications such as corticosteroid were thus considered unnecessary. The patient was placed on a calorie-restricted diet since obesity and its related factors are thought to play significant roles in the pathogenesis of renal injury. The oral administration of Losartan (50 mg/day) and Dipyridamol (300 mg/day) was started to correct the moderate hypertension and to decrease urinary protein excretion. Figure 3 shows the clinical course of the follow-up. Before hospitalization, his diet was estimated to range from 2,500-3,000 kcal per day. The estimated protein intake (EPI) as calculated by 24-hour urine collection was about 80 g/day. We thereafter started him with a diet menu consisting of about 1,800 kcal/day (30 kcal/kg ideal body weight) with a protein intake of 50 g/day (0.8 g/kg ideal body weight). As a result, he was able to successfully lose weight and the EPI after discharge was about 40-60 g/day. Twelve months later, his body weight and abdominal circumference were 73 kg (-13.1%) and 85 cm (-9.6%), respectively. In parallel, his blood pressure decreased to a level of optimal control. The plasma insulin concentration at the time of discharge was 22.1 IU/mL (normal range <13 IU/mL) and was normalized by two months. Urinary protein excretion markedly decreased to 1 g/24 hours after four months, 0.5 g/24 hours after five months and below 0.3 g/24 hours from seven months onward. His
renal function remained stable throughout the two-year follow-up; s-Cr was 1.3-1.4 mg/dL and 24-hour Ccr was 70-80 mL/min.

**Discussion**

Advanced age, hypertension, severe proteinuria, and renal impairment at presentation are known to be poor prognostic indicators of IgAN (6, 7). The present patient exhibited gradually increasing proteinuria and a slowly progressive renal impairment during the long-term follow-up. In addition, his blood pressure increased in parallel. Therefore, the patient was regarded to have had slowly progressive type IgAN for many years. However, the follow-up renal biopsy, which was carried out 25 years after the onset, did not show any glomerular inflammatory changes or IgA deposition. The histological findings only showed advanced chronic lesions such as an increased rate of global sclerosis and interstitial fibrosis. The remnant glomeruli showed marked increase in size and the small arteries showed typical findings of arteriolosclerosis. These findings suggest that the renal injury in this case, at least such injury which had occurred over the most recent few years, had thus been caused by non-immunologic mechanisms. Since this patient had moderate hypertension; i.e., about 130-150/90-100 mmHg, the possibility remains that the renal injury had simply been caused by nephrosclerosis. However, this patient showed marked decreases in proteinuria in association with decreases in body weight, abdominal circumference, blood pressure, and plasma insulin concentration. This finding is consistent with the currently proposed mechanism of obesity-related nephropathy in which several factors concomitantly contribute to its pathogenesis (1, 2).

As demonstrated in the third biopsy, it is likely that the activity of IgAN gradually diminished and finally resulted in a natural remission. In the literature that we searched, such a case showing disappearance of glomerular IgA deposition in the natural course has not been previously reported. There have been a few reports of repeat biopsies showing that glomerular deposition of IgA disappeared after steroid therapy of IgAN (8, 9), thus indicating that the degree of glomerular IgA deposition in each patient is correlated with immunological activity of the disease. Recent studies have demonstrated that IgA in the glomerular deposit in patients with IgAN is abnormally glycosylated (10) and potential receptors for IgA in the glomerular deposit have been identified (11). However, the mechanisms involved in such glomerular IgA deposition and the initiation or termination of inflammatory glomerular injury remain unclear.

The present case exhibited proteinuria and a slowly progressive renal impairment in spite of demonstrating only relatively mild obesity (BMI 28.4). In addition, the histological finding in the third biopsy did not show any FSGS lesions, which is a characteristic finding in obesity-related nephropathy other than glomerulomegaly (1). These findings may, in part, be explained by the presence of other potential causes of renal injuries such as decreased nephron mass due to the past history of IgAN and the renal injury was not caused by “pure” obesity-related nephropathy alone. The presence of metabolic syndrome or hyperinsulinemia is another possible explanation for the occurrence of renal injury with relatively mild obesity. Studies based on several community-based screening programs suggest that Japan has a higher prevalence of chronic kidney disease (CKD) than any other country (12). Therefore, such a factor of racial difference in renal functional reserve may be related to the
susceptibility to the loss of renal function when exposed to the additional causes of renal injury such as obesity. Finally, because it is well known that an excessive protein intake can accelerate renal injury through the induction of intraglomerular hypertension (13), it is possible to speculate that an excessive protein intake may thus have also played a role in the pathogenesis of renal injury in the present case.

At the time of the third biopsy, the rate of global sclerosis increased to 33%. On the other hand, glomerular density (non-sclerosed glomerular number/total cortical area) in each biopsy changed from 4.22-4.36/mm² to 1.33/mm²; i.e., about a 70% decrease (Fig. 1E). A decrease in the glomerular density and the renal function may be expected. On the other hand, only about a 40% decrease in the Ccr (130 to 80 mL/min) was observed between the first and the third biopsies. The discrepancy between the changes in the glomerular density and the renal function may be explained by compensatory glomerular hyperfiltration as reflected by a marked glomerular enlargement which was observed in the third biopsy. These findings are also consistent with the recent concept that nephron overwork and intraglomerular hypertension play a central role in the pathogenesis of obesity-related nephropathy (3, 4).

The patient was treated with a specific angiotensin-receptor antagonist (Losartan) in addition to a calorie-restricted diet. This might have resulted in an additive effect on reducing urinary protein excretion since recent studies suggest that the activation of the renin-angiotensin system is the major stimuli for an obesity-related increase in renal sodium reabsorption which leads to renal hyperperfusion and hyperfiltration (3, 14). However, obesity and its related metabolic factors contribute to the development of renal injury through multiple mechanisms, some of which are independent from the activation of the renin-angiotensin system (2-4, 14). Therefore, the mono-therapy of Losartan would not be expected to sufficiently reduce proteinuria in the present case. Furthermore, almost a complete disappearance of urinary protein excretion with a dramatic reduction in the nephron mass indicates the synergy of some as yet undetermined mechanisms between the functional changes induced by nephron loss and those induced by obesity (15).

References