Proteinuria rebound in IgA nephropathy associated with obesity-related glomerulopathy

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Abstract IgA nephropathy (IgAN), the most prevalent primary chronic glomerulonephritis worldwide, has three major risk factors: hypertension, proteinuria >1 g/day, and severe renal lesions. Obesity also portends a poor prognosis. A Japanese boy with IgAN showed nephrotic syndrome at presentation. Pathological features resembled those of membranoproliferative glomerulonephritis (MPGN), although IgA deposition differed from MPGN and IgAN. Combination therapy improved renal lesions, but rebound deterioration of proteinuria occurred in this patient, who had marked obesity and hypertension. Serial kidney biopsy specimens were compatible with obesity-related glomerulopathy (ORG). Rebound proteinuria was apparently attributable to ORG rather than relapse and flaring up of IgAN.

Keywords IgA nephropathy · Membranoproliferative glomerulonephritis · Nephrotic syndrome · Obesity-related glomerulopathy · Proteinuria

Introduction

In Japan, IgA nephropathy (IgAN) is the most common variety primary glomerulonephritis in both children and adults [1]. School mass urinary screening tests there discover about 70 % of childhood IgAN by chance hematuria

or proteinuria [1]. Nephrotic syndrome (NS) of presentation is uncommon [1, 2]. Once considered a benign disease, IgAN is now known to progress to chronic renal failure in adulthood in as many as 50 % of patients [3]. Obesity, hypertension, proteinuria, and severe pathological scores at diagnosis are other risk factors related to the progression of IgAN [4–6]. Herein, we report an obese patient with IgAN who presented with rebound of proteinuria after completing combination therapy. Repeated renal biopsies were necessary to ascertain whether or not relapse and flaring up of IgAN occurred. Rebound of proteinuria is not associated with relapse and flaring up of underlying IgAN, but with obesity-related glomerulopathy (ORG).

Case report

A Japanese patient, now 21 years old, first presented with IgAN at the age of 8 years. A school urinary screening test showed microscopic hematuria and heavy proteinuria. The patient had no petechiae on the legs. His weight was 37.0 kg, blood pressure (BP) 98/62 mmHg, and a body mass index (BMI) 20.7 kg/m². Laboratory data obtained at first admission are presented in Table 1. Percutaneous renal biopsy was performed, which revealed 20 glomeruli with two cellular crescents and one adhesion to Bowman's capsule. Moderate mesangial cell proliferation and increased mesangial matrix with lobulation were noted (Fig. 1a). The capillary lumen was narrowed. The capillary walls were thickened with a double contour (Fig. 1a). Interstitial fibrosis and tubular atrophy were not present. Immunofluorescence (IF) study revealed strong IgA and weak IgG; C3 showed coarse granular staining along the capillary walls and IgA also in the mesangium (Fig. 1b, c). Electron microscopy (EM) showed electron dense deposits

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Table 1 Laboratory data on first admission

Peripheral blood	
WBC	6120/mm ³
RBC	533 × 10 ⁴ /mm ³
Hb	15.3 g/dl
Hct	43.5 %
Platelet	32.8 × 10 ⁴ /mm ³
Blood chemistry	
TP	4.9 g/dl
Albumin	2.6 g/dl
AST	24 IU/l
ALT	21 IU/l
LDH	275 IU/l
T. cholesterol	269 mg/dl
BUN	15.0 mg/dl
Cr	0.4 mg/dl
UA	5.7 mg/dl
Na	140 mEq/l
K	4.0 mEq/l
Cl	103 mEq/l
Ca	8.6 mg/dl
P	5.2 mg/dl
Serological tests	
CRP	0.2 mg/dl
IgG	505 mg/dl
IgA	244 mg/dl
IgM	103 mg/dl
CH ₅₀	44 U/ml
C ₃	120 mg/dl
C ₄	19 mg/dl
Anti-nuclear antibodies	Negative
Anti-DNA antibodies	Negative
HBs antigen	Negative
Anti-HCV antibody	Negative
Urinalysis	
Gravity	1.010
pH	6.0
Protein	3+
Occult blood	3+
Glucose	Negative
Sediments	
RBC	40–50/HPF
WBC	1–5/HPF
Red cell casts	+
Urinary chemistry	
Protein	3.6 g/day
Urinary NAG	13.0 U/l
Urinary β ₂ -MG	240 μg/l
Creatinine clearance test	188.2 ml/min/1.73 m ²

NAG *N*-acetyl-beta-D-glucosaminidase, β₂-MG beta-2-microglobulin

(EDD) in the subepithelial, subendothelial, and mesangial areas (Fig. 1d). A diagnosis of IgAN with pathological features of membranoproliferative glomerulonephritis (MPGN) type I was made. Combination therapy was started as reported previously, with modifications [7–9]. The modified combination therapy consisted of prednisolone, mizoribine, heparin–warfarin, urokinase, dipyridamole, and candesartan cilexetil. Oral prednisolone, mizoribine, dipyridamole, and candesartan cilexetil were given, respectively, at dosages of 40, 150, 200, and 2 mg/day. The patient also underwent tonsillectomy to control upper respiratory infection.

After 2 years and 3 months, renal biopsy was performed a second time, revealing 20 glomeruli without obsolescent and crescentic glomeruli, adhesion to Bowman's capsule, and interstitial changes. The capillary walls showed punched out lesion and the double contour (Fig. 2). Mesangial matrix revealed mild expansion without lobulation. IF demonstrated weak staining of IgA in the mesangium. In addition, EM disclosed EDD in the paramesangium. Microscopic hematuria appeared and disappeared repeatedly. Proteinuria gradually decreased. The urine protein to creatinine ratio (UP/C) decreased to 1.0 g/g of creatinine (gCr) or less. Weight was increased to 58 kg. BMI was 27.4 kg/m² and BP 100/60 mmHg. A reduction of prednisolone was started. Three years and one month after onset of the disease, oral administration of both prednisolone and mizoribine was stopped.

One year after termination of medication, rebound deterioration of proteinuria occurred. Urinalysis showed 3+ to 4+ proteinuria and no hematuria. Serum creatinine was 0.6 mg/dl and UP/C 1.32 g/gCr. Weight was 86.6 kg, BMI 29.3 kg/m², and BP 110/53 mmHg. Diet was strongly recommended to reduce weight, although the patient refused to follow any recommended diet. At the age of 15 years, proteinuria was 3+, UP/C 1.50 g/gCr, weight 92.2 kg, BMI 31.3 kg/m², and BP 117/74 mmHg. Kidney function remained normal. The patient was referred to another hospital to consult a nephrologist. Unfortunately, the patient visited the hospital only a few times and arbitrarily quit the hospital. At the age of 17 years, the patient visited the hospital without an appointment because a urinary screening test in the high school detected severe proteinuria. His weight was 105 kg, BMI 35.5 kg/m², and BP 135/85 mmHg. Serum creatinine was 0.7 mg/dl, proteinuria 3+ without hematuria, and UP/C 1.20 g/gCr. Subsequently, the patient stopped coming to the hospital.

At the age of 21 years, a medical check pointed out severe obesity and proteinuria. Weight was now 105 kg, BMI 33.6 kg/m², and BP 150/73 mmHg. Serum creatinine was 0.78 mg/dl. Urinalysis showed 3+ isolated proteinuria with 0.55 g/gCr of UP/C. A third renal biopsy revealed 31

Fig. 1 First renal biopsy shows endocapillary proliferative glomerulonephritis with hypercellularity, increased mesangial cells and matrix, and the double-contoured appearance of the capillary loops (a) Periodic acid methenamine silver staining, magnification $\times 600$). Immunofluorescence micrographs show positive deposits of IgA

(b) and C3 (c) along the capillary walls (magnification $\times 400$). Electron micrograph shows subepithelial electron dense deposits (EDD) and a large hump-like EDD (asterisk) (d magnification $\times 5000$)

Fig. 2 Second renal biopsy shows punched out lesion and a double contour in the capillary walls (Periodic acid methenamine silver staining, magnification $\times 1000$)

glomeruli, in which one completely sclerosed glomerulus, another adhesion to Bowman's capsule, and no crescent were noted. Glomeruli were enlarged with a mild increase in mesangial cells and matrix (Fig. 3a). The glomerular diameter ($208.5 \pm 11.35 \mu\text{m}$, $194.8\text{--}224.5 \mu\text{m}$) was significantly larger than in normal controls ($168 \pm 12 \mu\text{m}$) [10]. The capillary lumen was patent. Focal tubular atrophy was present without interstitial fibrosis. Moreover, IF revealed weak linear staining of IgA and granular staining of IgM along the capillary walls. EM revealed neither effacement of the podocytes nor EDD (Fig. 3b). The glomerular basement membrane (GBM) thickness ($536 \pm 57 \text{ nm}$) was significantly greater than normal values for males ($330 \pm 50 \text{ nm}$) [11, 12] (Fig. 3c). Specimens from the third renal biopsy established a diagnosis of ORG. Unfortunately, the patient quit his company suddenly and never attended his appointments (Fig. 4).

Fig. 3 Third renal biopsy shows glomerulomegaly with slightly increased mesangial cells and matrix (**a** Periodic acid–Schiff staining, magnification $\times 400$). Bar 100 μm . Endothelial cells and podocyte foot processes maintain normal morphologic features without electron

dense deposits (**b** magnification $\times 3000$). Ultrastructural characteristics of the glomerular basement membrane (GBM). A uniformly wide GBM is located between fenestrated endothelial cells and the podocyte foot processes (**c** magnification $\times 20,000$). Bar 500 nm

Discussion

Results identified two important clinical issues. Histopathological features showed MPGN type I, but the pattern of IgA deposits was not typical idiopathic MPGN and IgAN. Rebound of proteinuria was associated with ORG.

First, histopathological features resembled MPGN type I, but the pattern of IgA deposits was not typical idiopathic MPGN and IgAN. Iitaka et al. reported similar cases with IgAN mimicking MPGN type I [13]. Both patients showed severe mesangial proliferation, mesangial deposits of IgA, and C3 along the capillary walls. Actually, IgAN was characterized by diffuse mesangial deposits of IgA, and often by IgG and C3 [13]. About 10–20 % of patients with IgAN also show IgA deposition in the capillary walls [1,

14]. Some reports have suggested that IgA deposition in the capillary walls with mesangial deposits is closely related to poor prognosis, but others did not [15]. Lupus nephritis was suggested as another candidate of MPGN type I, which also showed IgA deposits in the mesangium and in the capillary walls [13]. Our patient showed normal C3, negative anti-DNA antibodies, but no clinical features suggestive of lupus nephritis except for heavy proteinuria.

Second, rebound of proteinuria was associated with ORG, which manifested as obesity [BMI > 30], marked proteinuria without edema, and normal serum albumin concentration [6, 16]. Histologically, ORG was characterized by glomerular enlargement, mild hypercellularity, variable widening of mesangial regions, podocyte hypertrophy, thickening of GBMs, and at times focal segmental sclerosis [6, 16]. Actually, ORG was a secondary form of

Fig. 4 Clinical course. Anticoagulation therapy: intravenous administration of heparin 20 IU/kg/h and urokinase 60,000 IU/day

focal and segmental glomerulosclerosis (FSGS) [17]. Glomerulomegaly was the most striking feature of ORG, which differentiated this case from primary FSGS [17]. Third renal biopsy specimens showed glomerulomegaly, hypercellularity, mesangial expansion, and thickened GBM, all of which were well compatible with ORG. Obesity also portended a poor prognosis in patients with IgAN by the development of hypertension and progression to chronic renal failure [5, 6]. The concomitant presence of hypertension, dyslipidemia, hyperglycemia and/or insulin resistance, and inflammation in obesity exacerbated the renal injury from hyperfiltration [5, 6]. Proteinuria >1.3 g/ 1.73 m² and >14 % of glomerular crescents at the time of diagnosis were risk factors for persistent proteinuria [4]. Nephrotic-range proteinuria with 10 % glomerular crescents at diagnosis suggested that rebound deterioration of proteinuria was associated with relapse and flaring up of underlying IgAN. Fortunately, both the second and third renal biopsies revealed great improvement compared with the initial biopsy. Small cellular crescents in IgAN can subside with appropriate therapy [4]. The relapse and flaring up of IgAN were ruled out. Rebound of proteinuria was apparently attributable to ORG.

In conclusion, this patient with IgAN showed pathological features of MPGN at presentation. Combination therapy improved renal lesions, but rebound of proteinuria developed. The patient has become morbidly obese and hypertensive. Rebound of proteinuria appeared to be attributable to ORG rather than relapse and flaring up of IgAN. Prevention and modification of the lifestyle factors must be emphasized. Unfortunately, the patient would not act on our advice to take active measures to achieve sustained weight loss.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to the study described in this report.

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