Two cases of minor glomerular abnormalities with proteinuria disproportionate to the degree of hypoproteinemia

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Abstract We experienced two female cases of minor glomerular abnormalities with proteinuria disproportionate to the degree of hypoproteinemia. They did not have adequately large amounts of urine protein so as to cause nephrotic syndrome; however, we were unable to determine any cause of hypoproteinemia other than proteinuria. The renal pathology revealed foot process effacement, and hyaline droplet degeneration, suggesting urine protein hyperreabsorption in the proximal convoluted tubule. Therefore, we thought these cases involved pathophysiological conditions, such as minimal change nephrotic syndrome. In both cases, the hypoproteinemia improved following the administration of oral prednisolone. As in past reports, it is thought that the principal causative factor of hypoalbuminemia in patients with nephrotic syndrome is a catabolic reaction after the serum albumin filtered at the glomerulus is reabsorbed in the proximal tubule. In the present two cases, it is supposed that a large amount of urine protein was filtered in the primitive urine; however, the amount of final urinary protein did not reach the nephrotic range because most of it was reabsorbed in the proximal tubule and reabsorbed in the

blood after being disintegrated into amino acids by a catabolic reaction. Or we might simply observe the process before the case 1 got nephrotic syndrome and the healing process of nephrotic syndrome in the case 2.

Keywords Minor glomerular abnormalities · Non-nephrotic proteinuria · Hypoproteinemia · Hyaline droplet degeneration

Introduction

Nephrotic syndrome (NS) is a pathophysiological condition in which the urinary excretion of proteins increases as a result of changes in the selective permeability of the glomerular basement membrane with various findings, such as a large quantity of proteinuria (more than 3.5 g/day), hypoalbuminemia, dyslipidemia, and edema. However, a diagnosis of NS does not require patient to exhibit all of these symptoms, and initially, the diagnosis is made based on the presence of proteinuria at a nephrotic level [1]. We experienced two cases in which the patients did not exhibit adequately large quantities of urine protein to cause NS, but rather indicated hypoproteinemia, and were treated with steroids after excluding other diseases causing hypoproteinemia which improved the hypoproteinemia. To the best of our knowledge, no similar case has been reported to date. In addition, we take into consideration and report cases from the literature.

Case report

Case 1

A female in her 30s had no history of urine abnormalities on medical examinations. She noticed limb edema at 31 weeks

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of gestation at the time of her second pregnancy. She was found to have a serum total protein level (TP) 4.8 g/dL (48 g/L), a serum albumin level (Alb) 1.9 g/dL (19 g/L) and urine protein and was admitted to the gynecology department of our hospital, where our department was consulted. The patient's level of urine protein was 0.8–1.0 g/day and there were no complications of hypertension; therefore, we did not diagnose her with NS or pre-eclampsia. She did not exhibit exacerbation of the hypoproteinemia, and was therefore discharged. She delivered her second child at 39 weeks. Two weeks later, she developed exacerbation of edema and was hospitalized. A physical examination was remarkable only for bilateral lower limb edema. A laboratory evaluation (Table 1) revealed hypoproteinemia and hyperlipidemia. A urinalysis showed urine protein (2+), 882 mg/day. The protein intake (Maroni formula) was estimated to be 38.2 g/day (0.91 g/kg/day). Chest radiography, an electrocardiogram, ultrasonic cardiography, abdominal echo, and chest–abdominal CT showed no abnormalities. Gastrointestinal endoscopy, colonoscopy, capsule endoscopy and a small bowel series revealed no abnormalities, and there was no amyloid in the duodenum on a rectal biopsy. On protein leakage scintigraphy, there was no abnormal accumulation. A kidney biopsy was performed. Light microscopy revealed 15 glomeruli with no glomerular abnormalities (Fig. 1a), but showed hyaline droplet degeneration (Fig. 1b, c). There were no glomeruli in the immunofluorescent specimens. Electron microscopy showed more than 80 % foot process effacement with no electron-dense deposits (Fig. 1d). Therefore, we diagnosed the patient with minor glomerular abnormalities. Her clinical course is shown in Fig. 3a. We measured quantity of urine protein repeatedly to deny poor urine collection, but the laboratory data did not indicate a large enough quantity of urine protein to cause NS; however, the hypoproteinemia continued. We found no other causes of the hypoproteinemia. The patient's edema improved following hospitalization rest and diet therapy, and she was discharged. After the second discharge, the urine protein-creatinine ratio (U-Pro/Cr) was 0.7–2.8 g/g, the TP 4.2–5.1 g/dL (42–51 g/L) and Alb 1.3–2.2 g/dL (13–22 g/L) persisted. Ten months later from the second admission, U-Pro/Cr became 3.7 g/g, so she was hospitalized and we initiated treatment with oral prednisolone at a dose of 40 mg/day. Because the serum protein level exhibited a trend toward improvement, the dose of steroids was gradually tapered, and the parameters improved to U-Pro/Cr 0.1–0.5 g/g, TP 5.3–5.8 g/dL (53–58 g/L) and Alb 2.6–3.3 g/dL (26–33 g/L).

Case 2

A woman in her 30s had no history of urine abnormalities on medical examinations. She noticed bilateral lower limb edema in 20YY. Two months later, hypercholesterolemia

Table 1 Laboratory findings in admission

	Case 1	Case 2	
Peripheral blood			
White blood cell count	4.9	5.1	$\times 10^3/\mu\text{L}$
Red blood cell count	4.1	4	$\times 10^6/\mu\text{L}$
Hemoglobin	12.0	13.1	g/dL
Hematocrit	36.1	40.1	%
Platelets	257	330	$\times 10^3/\mu\text{L}$
Blood chemistry			
Total protein	4.4	4.2	g/dL
Albumin	1.5	1.5	g/dL
Aspartate aminotransferase	15	16	U/L
Alanine aminotransferase	12	12	U/L
Lactate dehydrogenase	217	210	U/L
Alkaline phosphatase	358	133	U/L
γ -Glutamyltransferase	9	7	U/L
Urea nitrogen	12	6.7	mg/dL
Creatinine	0.4	0.6	mg/dL
Uric acid	4.7	4.2	mg/dL
Total cholesterol	468	384	mg/dL
Triglycerides	346	146	mg/dL
Sodium	139	140	mEq/L
Potassium	3.6	3.8	mEq/L
Chloride	106	105	mEq/L
C-reactive protein	0.00	0.01	mg/dL
Immunological findings			
Rheumatoid factor	<3	<3	IU/mL
Antinuclear antibody	<40	<40	$\times$
Immunoglobulin G	391	476	mg/dL
Immunoglobulin A	270	129	mg/dL
Immunoglobulin M	105	246	mg/dL
C3 complement	1.27	1.02	mg/mL
C4 complement	0.34	0.23	mg/mL
Hepatitis B virus, surface antigen	(–)	(–)	
Hepatitis C virus antibody	(–)	(–)	
Urinalysis			
Protein	2+	2+	
Occult blood	+	(–)	
Glucose	(–)	(–)	
Sediments cast	(–)	(–)	
Urinary protein excretion	882	880	mg/day
Urinary protein-creatinine ratio	1.11	1.05	g/g
Creatinine clearance	179.0	144.2	mL/min
Selectivity Index	0.027	0.11	

and proteinuria were identified on a workplace medical examination. She was found to have TP 4.5 g/dL (45 g/L), serum total cholesterol 409 mg/dL (10.6 mmol/L) and urine protein (4+) at a primary hospital and was referred to our department. A physical examination performed on

Fig. 1 Renal biopsy findings of case 1. **a** Light microscopy revealed no glomerular abnormalities (periodic acid-methenamine silver stain $\times 400$). **b**, **c** Hyaline droplet degeneration (black arrows) in the proximal convoluted tubule epithelium (**b** hematoxylin–eosin stain

$\times 400$, **c** periodic acid-methenamine silver stain $\times 400$). **d** Electron microscopy showed more than 80 % foot process effacement (white arrows) with no electron-dense deposits

admission was remarkable only for bilateral lower leg edema. A laboratory evaluation (Table 1) revealed hypoproteinemia and hyperlipidemia. A urinalysis showed urine protein (2+), 880 mg/day. The protein intake (Maroni formula) was estimated to be 35.1 g/day. Like the case 1, image findings showed no abnormalities, so a kidney biopsy was performed. Light microscopy revealed 20 glomeruli with no glomerular abnormalities (Fig. 2a), but showed hyaline droplet degeneration (Fig. 2b, c). Immunofluorescent specimens exhibited no glomerular abnormalities. Electron microscopy showed more than 80 % foot process effacement with no electron-dense deposits (Fig. 2d). Therefore, we diagnosed the patient with minor glomerular abnormalities. Her clinical course is shown in Fig. 3b. We measured quantity of urine protein repeatedly to deny poor urine collection, but the laboratory data did not indicate a large enough quantity of urine

protein (U-Pro/Cr 0.4–1.0 g/g) to cause NS; however, the hypoproteinemia continued. We found no other causes of hypoproteinemia. During hospitalization, TP 4.1–4.6 g/dL (41–46 g/L) and Alb 1.5–1.9 g/dL (15–19 g/L) persisted, and we initiated treatment with oral prednisolone (40 mg/day). Because the levels of serum and urine protein showed improvements, the dose of steroids was gradually tapered. The laboratory parameters improved to a U-Pro/Cr 0.1–0.3 g/g, TP 6.5–6.7 g/dL (65–67 g/L) and Alb 4.0–4.3 g/dL (40–43 g/L).

Discussion

Causes of hypoproteinemia, except for NS, include a deficiency in the intake or supply of protein (starvation, malnutrition, etc.), a synthetic disturbance of protein (liver

Fig. 2 Renal biopsy findings of case 2. **a** Light microscopy revealed no glomerular abnormalities (periodic acid-methenamine silver stain $\times 400$). **b**, **c** Hyaline droplet degeneration (*black arrows*) in the proximal convoluted tubule epithelium (**b** hematoxylin–eosin stain

$\times 400$, **c** periodic acid-methenamine silver stain $\times 400$). **d** Electron microscopy showed more than 80 % foot process effacement (*white arrows*) with no electron-dense deposits

disease), asthenia due to proteolysis (severe infection, chronic wasting disease, etc.), an increase in protein demand (fever, hyperthyroidism, malignant tumors, etc.), leakage of proteins (blood loss, burns, puncture of ascites, protein-losing gastroenteropathy, etc.), deposition of proteins into organs (amyloidosis), hemodilution, etc. All of these findings were negative in both of the presented cases. Therefore, due to the pathophysiology that followed minimal change NS, we initiated treatment with prednisolone, and the hypoproteinemia and urinary protein showed a trend toward improvement.

Conventionally, based on analyses of primitive urine gathered according to the micropuncture method, a very small amount of albumin is known to leak through the glomerulus in healthy individuals [2], and almost 100 % of albumin in primitive urine is reabsorbed at the proximal tubule epithelium (PTE); therefore, almost no albumin is

included in the final urine. In recent years, a method that can visualize the dynamics of proteins in living bodies was developed, and the results of examinations of albumin metabolism dynamics in the kidneys using fluorescence-labeled albumin and two-photon microscopy were reported. According to the findings, even in the normal state, albumin leaks from the glomerulus, is taken into the PTE via endocytosis through receptors and collects in the blood [3]. The main causative factor of hypoproteinemia in patients with NS is hypoalbuminemia, which depends on the loss of serum albumin in the urine in large quantities. However, it is difficult to explain the occurrence of hypoalbuminemia only due to the quantity of albumin lost in the urine, and it is thought that the primary causative factor of hypoalbuminemia in patients with NS is the catabolic reaction that occurs when serum albumin is reabsorbed via the PTE following glomerular filtration [4–7].

Fig. 3 Clinical course (**a** case 1, **b** case 2)

As mentioned above, proteins that leak through the glomerulus combine with megalin and cubilin in the PTE and are taken into cells via endocytosis and reabsorbed in the blood after being disintegrated into amino acids in endosomes by lysosomal enzymes [8]. In addition, the possibility that the albumin taken into cells is collected via transcytosis has been reported. Studies that visualized and quantified the albumin degradation process in the kidneys using an albumin reagent (dye-quenched albumin) that emits fluorescence when disintegrated by protein degrading enzymes were recently reported. According to the results, after albumin is taken into the PTE, vesicular trafficking is carried out in the cell. On the other hand, approximately 40 % of proteins are disintegrated immediately [9]. The

failure of the recovery mechanism in patients with NS has received a lot of attention; as such failure may cause a high level of proteinuria.

The present two patients did not exhibit large enough quantities of urine protein to cause NS; however, the renal pathology showed hyaline droplet degeneration, indicating hyperfunctioning of urine protein reabsorption at the proximal convoluted tubule. The etymology of NS was originally named based on the findings of degeneration of the renal tubule epithelium recognized in this disease [10]. Based on the above findings, as in past reports, there is a possibility that a large quantity of urine protein was filtered in the primitive urine in the present two cases; however, the final quantity of urinary protein did not reach

the nephrotic range because the protein was reabsorbed within the proximal tubule and reabsorbed in the blood after being disintegrated into amino acids by a catabolic reaction. Or we might simply observe the process before the case 1 got NS and the healing process of NS in the case 2. In addition, protein leakages from the gastrointestinal edema (despite no abnormal accumulation on protein leakage scintigraphy) and to the stroma due to capillary hyperpermeability were considered to be causative factors of hypoproteinemia as in past literature [11]. In the case 1, the pregnancy and parturition might affect the hypoproteinemia too.

NS causes systemic edema due to a colloid osmotic decrease caused by hypoproteinemia, susceptibility to infection due to a decrease in immunoglobulin and thrombogenesis caused by hypercoagulability. Therefore, we believe that as in the present cases, patients who do not exhibit a large enough quantity of urine protein to cause NS, but demonstrate hypoproteinemia, can be treated aggressively with steroids and immunosuppressive drugs, as the pathophysiology of NS can present as hyaline droplet degeneration on renal pathology, excluding other diseases causing hypoproteinemia.

Conflict of interest The authors have declared that no conflict of interest exists.

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