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CASE REPORT

A rare case of nephrotic syndrome associated with Dent's disease: a case report

Shinichi Makino[1] · Maulana A. Empitu[1,2] · Toshimasa Naito[1] · Masayoshi Ishii[1] · Hanae Wakabayashi[1] · Chiwei Lee[1] · Masashi Aizawa[1] · Katsuhiko Asanuma[1]

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Abstract

Dent's disease is a rare X-linked condition caused by a mutation in *CLCN5* and *OCRL* gene, which impair the megalin-cubilin receptor-mediated endocytosis in kidney's proximal tubules. Thus, it may manifest as nephrotic-range low-molecular-weight proteinuria (LMWP). On the other hand, glomerular proteinuria, hypoalbuminemia, and edema formation are the key features of nephrotic syndrome that rarely found in Dent's disease. Here, we reported a man in his 30 s with Dent's disease presented with leg edema for 5 days. The laboratory results revealed hypoalbuminemia and a decrease of urine β2-microglobulin/urine protein ratio (Uβ2-MG /UP), indicating that the primary origin of proteinuria shifted from LMWP to glomerular proteins. The kidney biopsy revealed glomerular abnormality and calcium deposition in the renal medulla. Electron microscopy of the kidney tissue indicated extensive foot-process effacement of the glomerular podocytes and degeneration of tubular epithelium. After a combination of treatment with prednisolone and cyclosporine (CyA), the nephrotic syndrome was remitted. Given the atypical clinical presentation and the shift of LMWP to glomerular proteinuria in this patient, glomerulopathy and the Dent's disease existed separately in this patient.

Keywords Dent's disease · Nephrotic syndrome · Low-molecular-weight proteinuria (LMWP) · β2-microglobulin

Introduction

Dent's disease (OMIM #300009) is a rare X-linked recessive disorder affecting at least 250 families known worldwide [1]. The disease features low molecular weight proteinuria (LMWP), hypercalciuria, and progressive renal failure, which are caused by proximal tubule dysfunction [1, 2]. Since the proteinuria in Dent's disease is due to tubular dysfunction, the patients may develop nephrotic range proteinuria but rarely experience hypoalbuminemia.

In this report, we describe a case of a man in his 30 s with Dent's disease who developed new-onset of edema and hypoalbuminemia. Deviating from canonical features of Dent's disease, the patient developed glomerular abnormality that is indicated by extensive foot-process effacement. The composition of excreted protein also shifted from LMWP to glomerular proteinuria. Consequently, the glomerular proteinuria caused hypoalbuminemia. In overall, this report presented a rare case of Dent's disease and nephrotic syndrome (NS) with glomerular proteinuria and hypoalbuminemia. As other cases of Dent's disease-associated NS were reported in children, this report describes the first case of adult-onset NS in Dent's disease.

Case report

A man in his 30 s with Dent's disease presented new-onset edema for 5 days at the time of hospital admission. Bilateral pitting edema was found in his lower limbs, but not in other location. Body-weight increased by about 6 kg from a baseline of 63 kg. There is no abnormality of the vital signs. Review of systems revealed no cardiopulmonary abnormalities. Other physical and electrocardiography examinations findings were unremarkable.

✉ Katsuhiko Asanuma
kasanuma@chiba-u.jp

[1] Department of Nephrology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana Chuo-ku, Chiba-shi, Chiba 260-8677, Japan

[2] Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia

This patient has a record of proteinuria since he was 9 months old. His mother has a history of LMWP. When he was 6-year-old, the renal biopsy indicated normal glomeruli and calcium deposition in the renal tubule. At that time, he was diagnosed with Dent's disease by genetic testing, but detailed genetic data were not available. He had been followed as Dent's disease patients and treated with hydrochlorothiazide, potassium citrate, and sodium citrate hydrate for 30 years. Since then, the patient did not have any history of edema, NS, and other significant conditions. Six months before this hospitalization, the patient's laboratory data showed: serum albumin, 4.5 g/dL; serum creatinine, 0.98 mg/dL; urine protein, 1.95 g/g creatinine; urine low-molecular-weight protein β2-microglobulin (Uβ2-MG), 0.099 mg/mg creatinine.

At the time of admission, the laboratory findings revealed: serum albumin, 1.5 g/dL; serum creatinine, 1.2 mg/dL; total cholesterol, 456 mg/dL; Urine protein, 4 + and 27 g/g creatinine; urine erythrocytes, 2 + . The Uβ2-MG level was 0.10 mg/mg creatinine, near to patient's baseline. Other laboratory data are shown in Table 1. CT scan showed renal calcification (Fig. 1, arrow), consistent with medullary calcification due to Dent's disease.

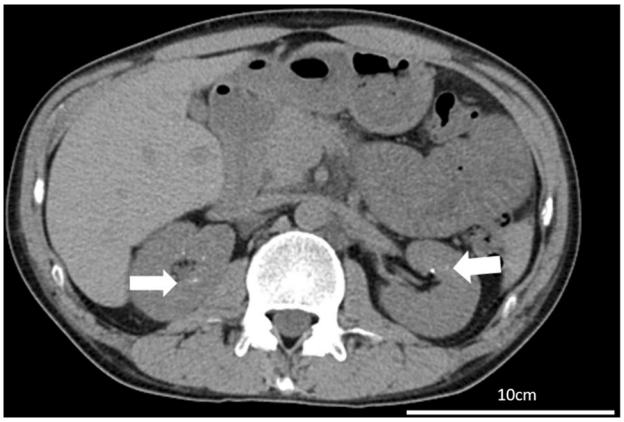

Fig. 1 CT image of the abdomen. CT scan showed renal calcification (arrow), which was consistent with medullary calcification due to Dent's disease. It also showed that small amounts of ascites, edematous wall thickening in the small intestine, and subcutaneous edema

Table 1 Patient's laboratory data

< Blood test data on admission >					
Total leukocyte	6800	/μL	IgG	949	mg/dL
Red Blood Cells	5780 × 10^3	/μL	IgA	211	mg/dL
Hemoglobin	17.2	g/dL	IgM	222	mg/dL
Hematocrit	50.5	%	IgE	4216	IU/mL
Mean corpuscular volume (MCV)	87.4	Fl	Serum C3	136	mg/dL
Platelet cells	216 × 10^3	/μL	Serum C4	31	mg/dL
AST	44	U/L	CH50	45.6	U/mL
ALT	41	U/L	Rheumatoid factor	3	IU/mL
Serum total protein	5.2	g/dL	CRP	0.06	mg/dL
Serum albumin	1.5	g/dL	HbA1c	5.3	%
Urine Acid	6.6	mg/dL	PT-INR	0.85	
Blood urea nitrogen	11	mg/dL	APTT	31	sec
Serum creatinine	1.2	mg/dL	D-dimmer	2.8	μg/mL
Serum sodium	139	mmol/L	Antinuclear antibody	Negative	
Serum potassium	3.6	mmol/L	PR3-ANCA	Negative	
Serum calcium	8.4	mg/dL	MPO-ANCA	Negative	

< Urine test data on admission >				
Glucose	–	Urine protein	1838	mg/dL
pH	7.0	Urine creatinine	75	mg/dL
Protein	4 +	protein/creatinine	27	g/gCre
Red blood cell	2 +	Urine calcium	0.4	mg/dL
White blood cell	–	Urine sodium	< 10	mmol/L
Tubular epithelial cell	3 +	Urine potassium	46	mmol/L
Cast, granular	1 +	Urine NAG	54.4	U/L
Cast, epithelia	1 +	Urine β2-MG	69,385	μg/L
Cast, waxy	1 +	Red blood cell	1 ~ 2	/HPF

The renal biopsy indicated a sclerosed glomerulus among the 29 obtained glomeruli. The tubules were cloudy and swelled, but there were no cellular crescents nor proliferation of mesangial cells (Fig. 2a). There was calcium deposition without any sclerotic arteriole in the renal medulla (Fig. 2b, arrow). There was also no significant reactivity for immunoglobulin G (IgG), IgM, IgA, C3, or C1q detected by immunofluorescence microscopy (data are not shown). Electron microscopy (EM) revealed extensive foot-process effacement (Fig. 3, arrowhead). No electron-dense deposits were identified in the mesangial region and basement membrane. In summary, renal biopsy indicated a minor glomerular abnormality and calcium deposition in the medulla. Thus, he was diagnosed with minimal-change nephrotic syndrome (MCNS) complicated with Dent's disease.

The timeline of the treatment, laboratory data, and changes in body-weight was shown in Fig. 4. The patient received 1000 mg of methylprednisolone from the day 4 to 7 of hospitalization and switched to 40 mg (0.8 mg/kg) oral prednisolone from day 8.

The proteinuria decreased right after the steroid treatment, but NS remission did not occur after 3 weeks of treatment. After combining the steroid with 125 mg cyclosporine (CyA) from day 25, the proteinuria gradually decreased. His body-weight decreased back to 60.3 kg and the edema disappeared on day 32. Two weeks after getting CyA, proteinuria was decreased to 2 g/g creatinine. The patient was discharged on day 38.

In order to assess the ratio of LMWP to total protein excretion in urine, we calculated the ratio of urine β2-MG / urine protein (Uβ2-MG/UP). At the time of admission, the Uβ2-MG /UP was decreased to 0.37% compared to 5.1% at the time of outpatient visit. As urine protein decreased during the treatment, the Uβ2-MG /UP was back to 6.83%, which is comparable to the ratio during outpatient follow up. The Uβ2-MG /UP was decreased during NS but increased along with the remission.

Six months after the administration, the dose of prednisolone was reduced to 10 mg. At that time, the patient had no visible edema. His laboratory findings showed that

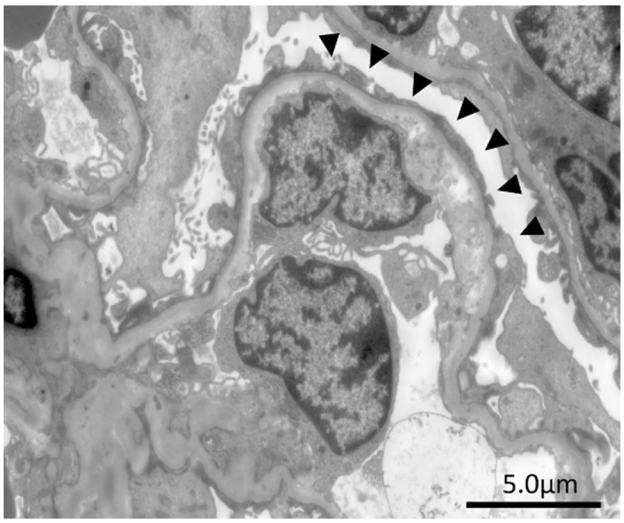

Fig. 3 Electron microscopic (EM) images of glomerulus. Foot-process effacement (arrow head) of podocytes were observed extensively in EM. No electron-dense deposits were identified in mesangial region and basement membrane

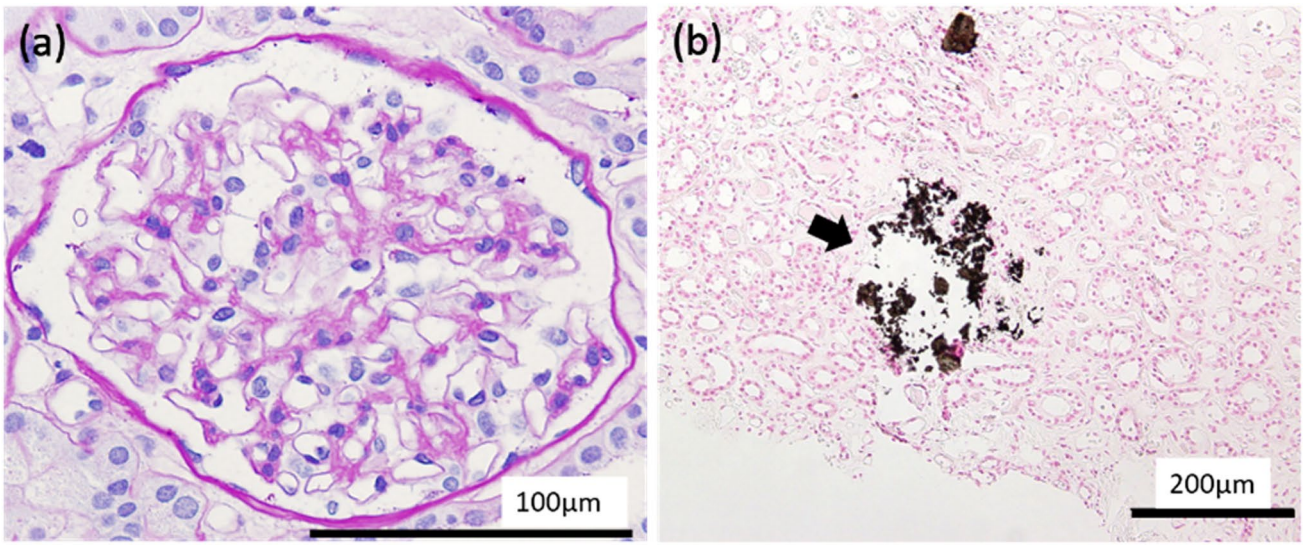

Fig. 2 Light microscopy images of kidney sample. **a** A glomerulus in Periodic acid–Schiff (PAS) staining of kidney biopsy sample. There were no cellular crescents and no proliferation of mesangial cells. **b** Von Kossa staining of kidney biopsy sample. Renal medulla with calcifications (arrows) was observed in the medullary interstitium

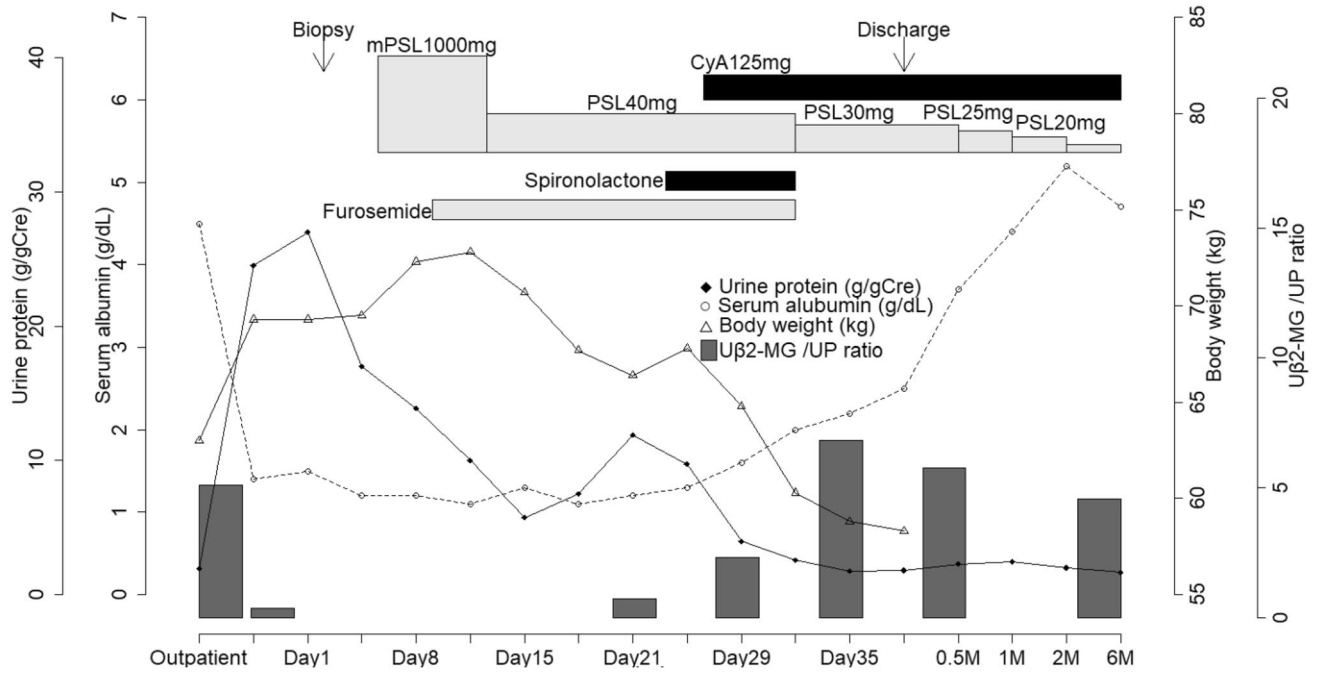

Fig. 4 The course of the treatment. The patient received 1000 mg of methylprednisolone from the day 4 to 7 and switched to 40 mg oral prednisolone from day 8. Because his body-weight had increased and the edema had worsened after steroid treatment, he received furosemide and spironolactone. The proteinuria decreased right after the steroid treatment, but NS remission did not occur after 3 weeks of treatment. After combining the steroid with 125 mg CyA from day 25, urine protein and body-weight decreased back to the baseline levels. The Uβ2-MG/UP was decreased during NS but increased along with the remission

serum albumin was 4.7 g/dL, and urine protein was 1.66 g/g creatinine. The Uβ2-MG/UP was 4.58%, consistent with the previous baseline value of the patient.

Discussion

The major feature of Dent's disease is LMWP caused by proximal tubule dysfunction. The tubular proteinuria composes of LMWP such as β2-MG (12 kDa) [3], α1-MG (30 kDa) [4], and retinol-binding protein (RBP) (21 kDa) [5]. On the other hand, glomerular proteinuria mainly composes of albumin (65 kDa).

Patients with Dent's disease who develop nephrotic-range proteinuria usually have tubulopathy and/or additional glomerulopathy such as secondary FSGS or focal global glomerulosclerosis [6–10], characterized by the absence of edema or hypoalbuminemia [1]. However, the present patient experienced subacute weight gain, new-onset edema of lower extremities, and hypoalbuminemia. Podocytes' foot-process effacement was reported in 57% of the Dent's disease, but the majority of it was segmental and mild [6], whereas extensive foot-process effacement was observed in this case. From these findings, we considered that the NS was due to glomerular disease that developed independently of Dent's disease in this patient. However, we could not deny the possibility that secondary FSGS or tubulopathy from Dent's disease could affect the seriousness of the therapeutic response. CIC-5 encoded by *CLCN5* is known to be involved in LMWP endocytosis but also albumin endocytosis in renal tubules [11]. Also, it was reported that the expression level of CIC-5 was upregulated in glomeruli of proteinuric patients, and it may be involved in albumin endocytosis in podocytes [10]. Thus, the background of Dent's disease might be exacerbator in this patient.

In Dent's disease, the most commonly used parameter to determine LMWP is β2-MG, compared to others such as α1-MG, and RBP [1]. Norden et al. reported that the average of urine β2-MG among Dent's disease patients was 0.10 mg/mg creatinine [12]. In our case, the urine β2-MG at the time of outpatient examination was consistent at the level of 0.099 mg/mg creatinine. When the patient had a severe episode of proteinuria and hypoalbuminemia, the urine β2-MG remained unchanged at 0.092 mg/mg creatinine. The unchanged level of urine β2-MG despite the increased albuminuria indicated that the LMWP and the glomerular proteinuria existed separately in this patient.

There have been few cases of combined Dent's disease and NS [13]. Guohua He et al. reported that a urine α1-microglobulin/urine albumin ratio could be used as a parameter to distinguish between LMWP due to Dent's disease and albuminuria caused by NS [13]. We calculated

the Uβ2-MG/UP ratio to assess the rate of LMWP to total protein excretion in the urine. Before the patient developed the NS, the Uβ2-MG/UP was 5.1%. When the patient developed the NS, the ratio was decreased to 0.37%. When the patient's urine protein decreased back to its usual level, the ratio was increased to 6.8%. Thus, the primary origin of proteinuria shifted from LMWP to glomerular proteins. The Uβ2-MG/UP was also consistent with the progression of NS. Although the Uβ2-MG/UP might be underestimated because the urine β2-MG is degraded in the case of acidic urine, the Uβ2/UP can be used to monitor the relapse of NS.

In conclusion, this report presented a rare case of NS in Dent's disease. In contrast to the typical manifestation of Dent's disease that mostly features LMWP instead of albuminuria, the patient in our case experienced the typical triad of NS: pitting edema, albuminuria, and hypoalbuminemia. This report also showed a potential clinical use of the Uβ2-MG/UP to monitor the course of NS in Dent's disease patients.

Compliance with ethical standards

Conflicts of interest No author has a direct conflict of interest that is relevant to this study. Outside the contents of the study, Katsuhiko Asanuma received research funding from Mitsubishi Tanabe Pharmaceutical Corporation.

Informed consent Written informed consent was obtained from the patients, including consent to participate in a clinical study approved by Ethics Committee of Chiba University (approval number: Life-856) and to publish the findings.

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