INTERNAL MEDICINE

□ CASE REPORT □

Non-uniform Progression of Chronic Tubulointerstitial Nephritis and Widespread Nephrocalcification in a Patient with Anorexia Nervosa

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Abstract

Although patients with anorexia nervosa (anorexia) are known to show tubulointerstitial nephritis (TIN), the pathophysiology of its progression is not fully understood. We herein report a 31-year-old woman with anorexia who showed acute exacerbation of chronic kidney disease. Renal biopsy showed non-uniform chronic TIN; some areas were obsolete lesions and other areas were active lesions. In addition, many calcium-containing crystals were widely deposited in the distal tubules. The results suggest that chronic TIN in the setting of anorexia does not uniformly progress and that not only TIN but also widespread calcification of distal tubules might aggravate the renal function of anorexia patients.

Key words: anorexia nervosa, chronic tubulointerstitial nephritis, nephrocalcification, renal biopsy

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Introduction

Anorexia nervosa (anorexia) is an eating disorder characterized by a distorted perception of the body shape and an intense fear of gaining weight, which results in abnormally low body weight and various medical complications (1, 2). Previous reports have shown that as many as 70% of anorexia patients had associated renal problems, including a decreased glomerular filtration rate, impaired concentrating ability, and electrolyte abnormalities (3-5). The pathophysiology of chronic kidney disease (CKD) in anorexia patients is not yet fully understood, although several previous renal biopsy reports revealed chronic tubulointerstitial nephritis (TIN) that is probably due to prolonged hypokalemia (4-6). We herein present the renal biopsy findings of an anorexia patient who showed acute exacerbation of CKD.

Case Report

The patient was a 31-year-old woman who had been suffering from an eating disorder since she was 13 years old. She had been vomiting repeatedly on purpose and abused diuretics and alcohol. At age 26, hypokalemia (serum potassium of 2.8 mmol/L) and metabolic alkalosis (serum bicarbonate of 41.5 mmol/L) were noted, and she was introduced to our outpatient clinic. At the first visit, she showed chronic kidney disease (serum creatinine of 1.18 mg/dL) and hyperuricemia (serum uric acid of 11.7 mg/dL). No family history of kidney diseases such as Alport syndrome was found. She had been prescribed potassium chloride tablets and an antihyperuricemic agent (febuxostat) at the outpatient clinic, but she did not come to the hospital regularly. She did not take any prescribed medications regularly and probably took non-prescribed medications such as diuretics in secret. When she came to the hospital, her serum potassium level was 2.5-3.5 mmol/L. She sometimes had acute kidney injury due to dehydration, which soon resolved after fluid replacement, and her serum creatinine level had been stable around 1.5-2.0 mg/dL. She did not show any urinary tract infection. However, at age 31, she complained of a gout attack and showed acute kidney injury (serum creatinine of 8.95 mg/

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Table. **Laboratory Tests.**

Hematological tests			**Blood gas analyses**		
WBC	7.47	$\times 10^3/\mu L$	pH	7.484	
Neutro	62	%	$PaCO_2$	73.9	mmHg
Lymph	28.9	%	HCO_3	55.5	mmol/L
Mono	4.8	%	BE	28.3	mmol/L
Eosino	3.6	%	**Serological tests**		
Baso	0.7	%	CRP	1.33	mg/dL
RBC	3.42	$\times 10^4/\mu L$	ANA	negative	
Hb	10.2	g/dL	IgG	1,265	mg/dL
Hct	30.9	%	IgA	426	mg/dL
MCV	90.4	fL	IgM	100	mg/dL
Plt	27	$\times 10^4/\mu L$	C3	100	mg/dL
Biochemistry tests			C4	31	mg/dL
TP	8.1	g/dL	ASO	153	U/mL
Alb	3.9	g/dL	MPO-ANCA	negative	
T-chol	207	mg/dL	PR3-ANCA	negative	
BUN	39.3	mg/dL	Anti-GBM	negative	
Cre	8.74	mg/dL	**Urinalysis**		
eGFR	5.0	$mL/min/1.73\ m^2$	pH	8.5	
UA	5.3	mg/dL	Specific gravity	1.011	
Na	137	mmol/L	Protein	(3+)	
K	3.0	mmol/L	Protein (collection)	1.35	g/day
Cl	77	mmol/L	Occult blood	(±)	
Ca	9.4	mg/dL	Selectivity index	0.25	
IP	6.6	mg/dL	BJP	negative	
FBS	108	mg/dL	Urine β2MG	61,952	μg/L
			Sediments	Epithelial casts Crystal casts	

WBC: white blood cell, Neutro: neutrophil, Lymph: lymphocyte, Mono: monocyte, Eosino: eosinophil, Baso: basophil, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, Plt: platelet, TP: total protein, Alb: albumin, T-chol: total-cholesterol, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, UA: uric acid, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, IP: inorganic phosphorus, FBS: fasting blood sugar, pH: power of hydrogen, $PaCO_2$: partial pressure of arterial carbon dioxide, HCO_3: bicarbonate, BE: base excess, CRP: C-reactive protein, ANA: anti-nuclear antibody, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, ASO: anti-streptolysin O, ANCA: anti-neutrophil cytoplasmic antibody, Anti-GBM: anti-glomerular basement membrane antibody, BJP: Bence Jones protein, β2MG: β2-microglobulin

dL). Ultrasound revealed that both of her kidneys were slightly atrophic (major axis was around 9.5 cm), and no hydronephrosis was found. We gave her fluid replacement therapy, and her kidney function recovered, and her serum creatinine level dropped to 7 mg/dL, but it did not recover further.

As the exacerbation of the renal function was acute, there was a possibility of acute drug-induced TIN, which can respond to steroid therapy. The patient denied any non-prescription drug use and hoped to discover the reason for the acute kidney injury. Therefore, we conducted renal biopsy after explaining the risks. On the day of biopsy, her height was 157 cm, weight was 44.6 kg, and body mass index (BMI) was 18.1 kg/m^2. Her body temperature was 36.5℃, blood pressure was 112/52 mmHg, pulse rate was 78 beats per minute, and peripheral oxygen saturation was 97% (room air). She did not show pretibial edema. Laboratory tests (Table) showed blood urea nitrogen (BUN) of 39.3 mg/dL, serum creatinine of 8.74 mg/dL, serum potassium of 3.0 mmol/L, serum chloride of 77 mmol/L and serum bicarbonate of 55.5 mmol/L. Anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA) and anti-glomerular basement membrane (GBM) antibody were negative, and the serum complement (C3, C4 and CH50) levels were not decreased. The urine protein was 1.35 g/day (selectivity index was 0.25), and urine β2-microglobulin was 61,952 μg/L. The urine sediment contained 5-9 red blood cells/high power field and some crystal casts with no uric acid salt.

Renal biopsy findings

The renal biopsy specimens included 41 glomeruli. Fifteen glomeruli had normal features, 23 showed complete sclerosis, and 2 showed segmental sclerosis (Fig. 1A). One glomerulus showed perihilar segmental sclerosis (Fig. 1B). On immunofluorescent staining, the glomeruli were negative for IgG, IgA, IgM, C1q, C3, C4, and fibrinogen. On electron microscopy, collapsed glomerular capillaries and wrinkled glomerular basement membranes were noted. Epimembranous depositions were not found. Foot process fusions were not obvious (Fig. 1C and D).

Numerous lymphocytes and plasma cells had broadly infiltrated the interstitium. No eosinophilic infiltration was found (Fig. 1E). In most areas, interstitial expansion and tubulitis were found. The tubular structures were intact, and there was scattered mild lymphocytic infiltration of the tubules (Fig. 1F, lower side). In some areas, a collection of atrophic tubules with thickened basement membranes and flattened epithelia with complete loss of the brush border were found (Fig. 1F, upper half).

A number of crystals were widely deposited in the distal tubules. The crystals, which were stained basophilic by Hematoxylin and Eosin staining (Fig. 2A) and black by von Kossa stain, included calcium crystals (Fig. 2B). On electron microscopy, the crystals in the distal tubules had a high density (Fig. 2C and D).

These histologic findings were considered indicative of protracted active TIN, secondary glomerulosclerosis, and tubular calcium depositions.

Clinical course

Renal biopsy showed TIN with calcification of the distal tubules but did not reveal the exact reason for the acute exacerbation of CKD. Given the observation of active TIN with interstitial expansion and tubulitis, we recommended that she undergo steroid therapy, but she declined. We continued conservative treatment, and her renal function temporarily improved, as her serum creatinine dropped to 4 mg/dL in 6 months. Since then, her renal function has fluctuated, occasionally approaching end-stage kidney disease.

Discussion

The renal biopsy findings of this patient provide two important clinical suggestions: Chronic TIN caused by ano-

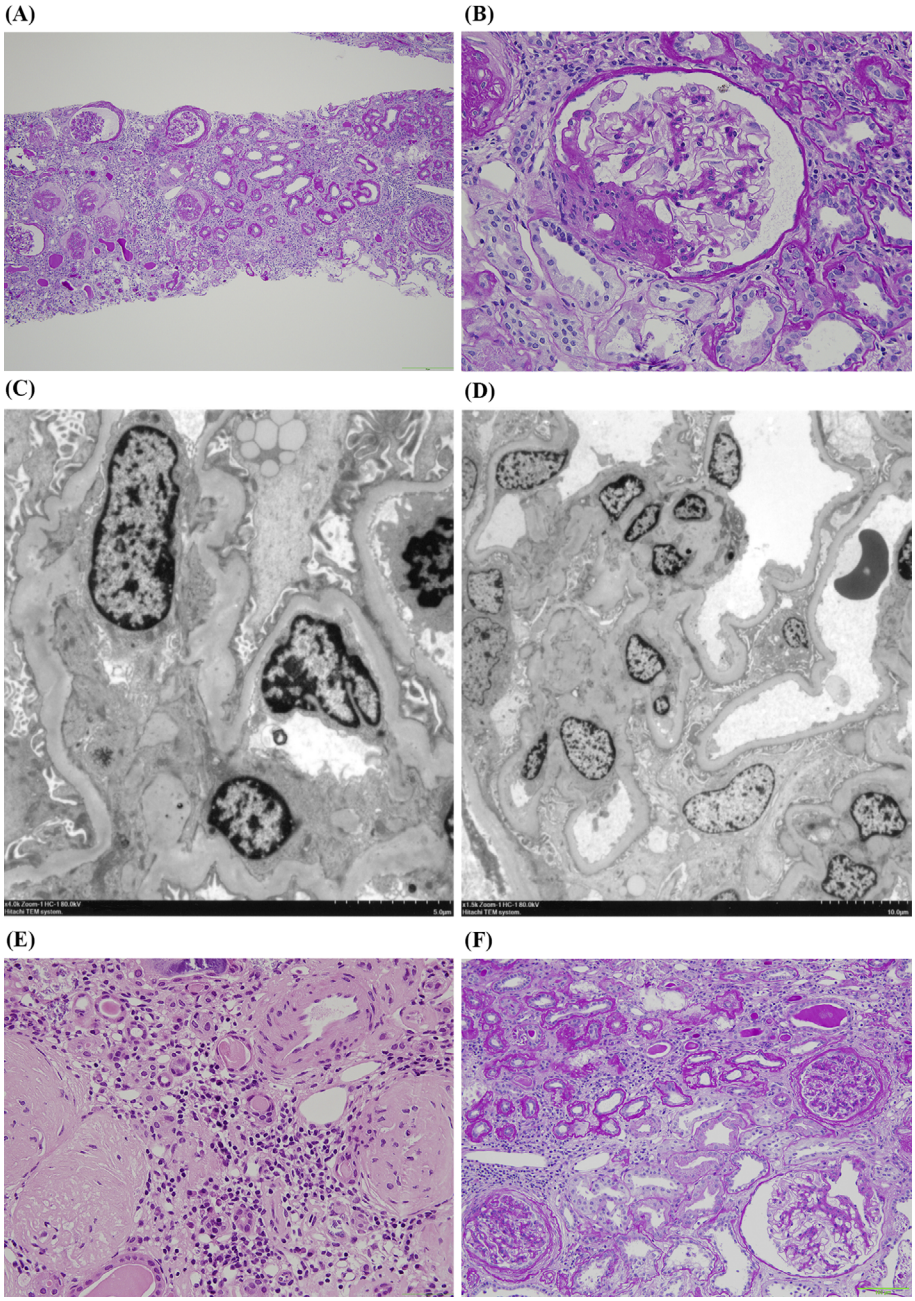

Figure 1. **Gradual progression of tubulointerstitial nephritis. (A) Chronic tubulointerstitial nephritis (TIN) and collapse of glomeruli; Periodic acid-Schiff stain (×100). (B) Secondary perihilar glomerulosclerosis; Periodic acid-Schiff stain (×400). (C, D) Collapsing glomeruli on electron microscopy (×4,000, ×1,500). (E) Widespread infiltration of many lymphocytes and plasma cells into the interstitium; Hematoxylin and Eosin staining (×400). (F) The tubular basement membranes (TBMs) were thickened, and the epithelium was flattened with complete loss of the brush border (obsolete TIN, upper half). Lymphocytes infiltrated into the tubules, but the structures of the tubules were intact (active TIN, lower half); Periodic acid-Schiff stain (×400).**

rexia does not uniformly progress, and not only TIN but also widespread calcification of the distal tubules can aggravate the renal function of anorexia patients.

First, chronic TIN caused by anorexia does not uniformly progress. Renal biopsy of this patient revealed that some areas were obsolete lesions and other areas were active lesions. It was previously reported that anorexia was associated with chronic TIN (5-7). The main cause of chronic TIN is considered to be prolonged hypokalemia, which may be caused by a deficit of potassium in the diet, diuretic abuse, repeated vomiting, and stimulation of the renin-angiotensin-aldosterone system (8). Prolonged hypokalemia is known to produce vacuolar lesions in the epithelial cells of tubules (9), ultimately leading to TIN (4, 10, 11), the mechanism of which has been partially clarified by animal experiments (12-15). Since the present patient showed serum po-

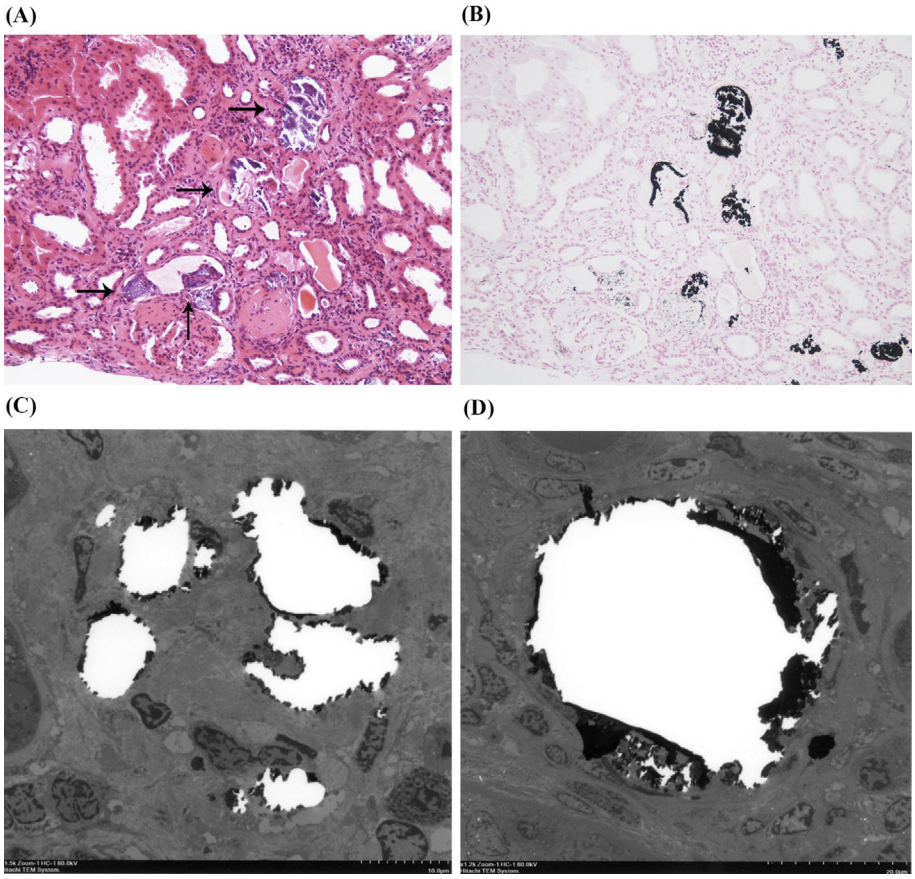

Figure 2. Widespread calcification of the distal tubules. (A) A number of crystals broadly deposited in the distal tubules were stained basophilic by Hematoxylin and Eosin staining (×400). The black arrows indicate the location of the crystals. (B) The crystals were stained black by von Kossa stain (×400). (C, D) The crystals in the distal tubules had a high density on electron microscopy (×1,500, ×1,200).

tassium of 2.5-3.5 mmol/L, prolonged hypokalemia might have an important role in the progression of TIN. However, considering that the chronic TIN of this patient did not uniformly progress, prolonged hypokalemia might not be the only factor that induced TIN. It was previously reported that not only prolonged hypokalemia but also chronic reduced kidney perfusion, repeated urinary tract infection, and drug abuse were related to TIN in anorexia patients (8). This patient's TIN might have been induced by many factors related to anorexia. The renal function might recover after steroid use because of the existence of active TIN, but steroid therapy has not been used to treat chronic TIN of anorexia patients in previous reports.

Second, not only TIN but also widespread calcification of the distal tubules might have aggravated the renal function of anorexia patients. Renal biopsy of this patient showed that a number of crystals, including calcium ones, were widely deposited in the distal tubules. Since the serum calcium level and the amount of urine calcium (0.06 g/day) were within the normal range, the likelihood of diseases that cause hypercalciuria, such as hyperparathyroidism and sarcoidosis, was low. Previous reports have suggested that anorexia patients tend to show nephrocalcinosis (16-18). Furosemide inhibits Na^+-K^+-$2Cl^-$ cotransporters in the thick ascending limb of the loop of Henle, increases the intraluminal calcium concentration, and causes nephrocalcinosis (19), although we did not determine the exact amount of diuretics this patient had been taking or for how long. An autopsy report of an anorexia patient suggested that an enhanced renin-angiotensin system inhibited NaPi-IIa cotransporters in the proximal tubules and Ca^{2+}-ATPase in the thin limb of the loop of Henle, causing nephrocalcinosis (17, 18). These previous reports did not detect an association between nephrocalcinosis and aggravation of the renal function. However, renal biopsy of this patient showed that the deposition of many crystals in the distal tubules was very widespread, which might have contributed to the aggravation of the renal function by itself.

In conclusion, chronic TIN caused by anorexia does not uniformly progress, and not only TIN but also widespread calcification of the distal tubules might aggravate the renal function of anorexia patients. An accumulation of further cases is needed to understand the progression of CKD caused by anorexia.

The authors state that they have no Conflict of Interest (COI).

References

1. American Psychiatric Association. Treatment of patients with eating disorders, third edition. American Psychiatric Association. Am J Psychiatry **163**: 4-54, 2006.
2. Mehler PS. Diagnosis and care of patients with anorexia nervosa in primary care settings. Ann Intern Med **134**: 1048-1059, 2001.
3. Brotman AW, Stern TA, Brotman DL. Renal disease and dysfunction in two patients with anorexia nervosa. J Clin Psychiatry **47**: 433-434, 1986.
4. Riemenschneider T, Bohle A. Morphologic aspects of low-potassium and low-sodium nephropathy. Clin Nephrol **19**: 271-279, 1983.
5. Abdel-Rahman EM, Moorthy AV. End-stage renal disease (ESRD) in patients with eating disorders. Clin Nephrol **47**: 106-111, 1997.
6. Arimura Y, Tanaka H, Yoshida T, et al. Anorexia nervosa: an important cause of chronic tubulointerstitial nephropathy. Nephrol Dial Transplant **14**: 957-959, 1999.
7. Hampton P, Graham KA, Millar M, McCluskey S, Goodship TH. Anodipsia nervosa a variant of anorexia in patients with end-stage renal disease. Nephrol Dial Transplant **17**: 942-943, 2002.
8. Bouquegneau A, Dubois BE, Krzesinski JM, Delanaye P. Anorexia nervosa and the kidney. Am J Kidney Dis **60**: 299-307, 2012.
9. Schwartz WB, Relman AS. Effects of electrolyte disorders on renal structure and function. N Engl J Med **276**: 383-389, 1967.
10. Cremer W, Bock KD. Symptoms and course of chronic hypokalemic nephropathy in man. Clin Nephrol **7**: 112-119, 1977.
11. Menahem SA, Perry GJ, Dowling J, Thomson NM. Hypokalaemia-induced acute renal failure. Nephrol Dial Transplant **14**: 2216-2218, 1999.
12. Tolins JP, Hostetter MK, Hostetter TH. Hypokalemic nephropathy in the rat. Role of ammonia in chronic tubular injury. J Clin Invest **79**: 1447-1458, 1987.
13. Reungjui S, Roncal CA, Sato W, et al. Hypokalemic nephropathy is associated with impaired angiogenesis. J Am Soc Nephrol **19**: 125-134, 2008.
14. Suga S, Mazzali M, Ray PE, Kang DH, Johnson RJ. Angiotensin II type 1 receptor blockade ameliorates tubulointerstitial injury induced by chronic potassium deficiency. Kidney Int **61**: 951-958, 2002.
15. Tsao T, Fawcett J, Fervenza FC, et al. Expression of insulin-like growth factor-I and transforming growth factor-β in hypokalemic nephropathy in the rat. Kidney Int **59**: 96-105, 2001.
16. Roberts MA, Thorpe CR, Macgregor DP, Paoletti N, Ierino FL. Severe renal failure and nephrocalcinosis in anorexia nervosa. Med J Aust **182**: 635-636, 2005.
17. Unuma K, Tojo A, Harada K, et al. Autopsy report on pseudo-Bartter syndrome with renal calcification induced by diuretics and diet pills. BMJ Case Rep **2009**: bcr12.2008.1380, 2009.
18. Tojo A, Unuma K, Harada K, Yoshida K, Fujita T. Localization and mechanism of nephrocalcinosis in pseudo-Bartter's syndrome. Kidney Int **77**: 831, 2010.
19. Sayer JA, Carr G, Simmons NL. Nephrocalcinosis: molecular insights into calcium precipitation within the kidney. Clin Sci (Lond) **106**: 549-561, 2004.