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

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/dL).
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 widely 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-
Anorexia 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-
K. 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).
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