

[CASE REPORT]

Nutcracker Syndrome with the Superimposition of Thin Basement Membrane Syndrome

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Abstract:

A 21-year-old woman was referred to our hospital because of proteinuria and hematuria. She had occasional flank pain. A renal biopsy was performed and revealed a thin basement membrane. Therefore, she was diagnosed with thin basement membrane disease. However, the frequency of her flank pain increased. Since her left kidney was slightly larger than the right, nutcracker syndrome (NCS) was suspected. Renal vein ultrasonography and venography were performed, and NCS was confirmed. Her hematuria was multifactorial, and NCS can go unnoticed if there is a comorbidity that also causes hematuria.

Key words: hematuria, flank pain, nutcracker syndrome, left renal vein entrapment, thin basement membrane disease

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Introduction

Nutcracker syndrome (NCS) is caused by left renal vein entrapment by the superior mesenteric artery and abdominal aorta, resulting in left renal vein hypertension and intermittent hematuria and flank pain. NCS is usually suspected when intermittent hematuria is observed; however, in the presence of a comorbidity that can also cause hematuria, NCS can go unnoticed, as the diagnosis requires renal vein ultrasonography or angiography, both of which are not commonly performed unless NCS is suspected.

We experienced a case of NCS with thin basement membrane disease (TBMD), which also causes hematuria and occasionally causes intermittent flank pain. No other report has described the coexistence of NCS and TBMD with pathological and radiographic confirmation, presumably because of the difficulty diagnosing one disease in patients comorbid with the other.

Case Report

A 21-year-old woman was referred to our hospital for proteinuria with hematuria. Her urine test had become positive for proteinuria and hematuria over 10 years earlier, and gross hematuria had been occasionally seen for several years. Both her father and mother had histories of proteinuria and hematuria, but there was no family history of end-stage kidney disease. Her body mass index was 18.9 kg/m², and her blood pressure was 124/68 mmHg. Her urinary protein was 1.4 g/g creatinine, and her urine sediment showed 10-19 red blood cells per high-power field. Her serum creatinine was not elevated. She also complained of frequent flank pain without gross hematuria. The results of a physical examination and laboratory tests are shown in Table. Abdominal ultrasound as a pre-biopsy test showed an almost normal morphology in her kidneys. The sizes of the right and left kidneys were 10.9×4.3 and 11.6×5.2 cm, respectively.

A renal biopsy was performed for the left kidney, and the

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Table. Patient Characteristics at the Time of the Renal Biopsy.

Urinary test		Blood chemical values		Hematological values	
Urinary protein	129 mg/gCre	Albumin	4.4 g/dL	White blood cell count	7,400 / μ L
Urinary sediment- RBC	10-19 /HPF	Total cholesterol	167 mg/dL	Red blood cell count	401 \times 10 ⁴ / μ L
NAG	3.4 U/gCre	Blood urea nitrogen	13.6 mg/dL	Hemoglobin	11.9 g/dL
		Creatinine	0.48 mg/dL	Platelet count	17.2 \times 10 ⁴ / μ L
Urinary Sediment		eGFR	133.4 mL/min/1.73m ²		
Hyaline Cast	1-4 /WF	Uric acid	4.1 mg/dL	Immunological study	
Granular Cast	1-4 /WF	Sodium	138 mmol/L	IgG	1,526 mg/dL
		Potassium	3.9 mmol/L	IgA	136 mg/dL
		Chloride	102 mmol/L	ANA	Negative
		C-reactive protein	0.04 mg/dL	Complement 3	93 mg/dL
				Complement 4	25 mg/dL
				CH50	50.9 U/mL

ANA: antinuclear antibody, CH50: 50% hemolytic complement activity, eGFR: estimated glomerular filtration rate, NAG: N-acetyl- β -D-glucosaminidase, RBCs: red blood cells

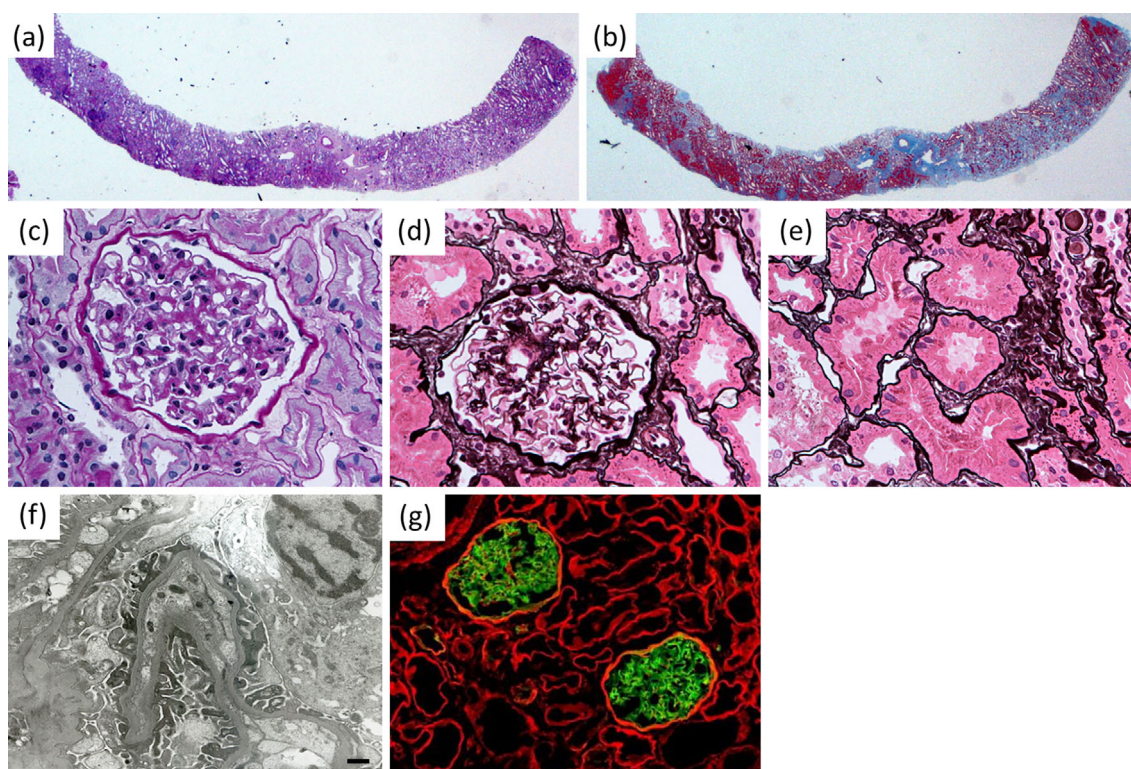


Figure 1. Images of the renal biopsy. (a) Periodic acid-Schiff staining image, \times 20. (b) Azan staining image, \times 20. (c) Periodic acid-Schiff staining image, \times 400. (d, e) Periodic acid-methenamine silver staining image, \times 400. (f) Electron microscopy image, \times 10,000. Scale bar: 500 nm. (g) Immunofluorescence image. Red: Type 4 collagen α 2, Green: Type 4 collagen α 5.

glomeruli seemed slightly collapsed. However, there were only minor glomerular abnormalities on light microscopy (Fig. 1a-e). The fibrotic area accounted for <10% of the cortex, and no other major abnormality existed. No abnormalities indicative of renal congestion were found in the arteries, veins, or lymphatic vessels. The glomerular basement membrane was revealed to be thin on electron microscopy (Fig. 1f). No lack of type 4 collagen α 5 subunit was seen (Fig. 1g). Therefore, she was diagnosed with TBMD.

Thereafter, she was observed with regular hospital visits.

However, the frequency of her flank pain increased and could not be explained by TBMD. Since her flank pain was localized at her left side and exacerbated after prolonged standing, left renal vein entrapment by the abdominal aorta and superior mesenteric artery was suspected and subsequently documented on renal vein ultrasonography (Fig. 2). Enhanced computed tomography was also performed, and entrapment of the renal vein was also evident (Fig. 3). No other abnormalities that could cause flank pain and hematuria, such as urinary tract stone, were found. Her flank pain

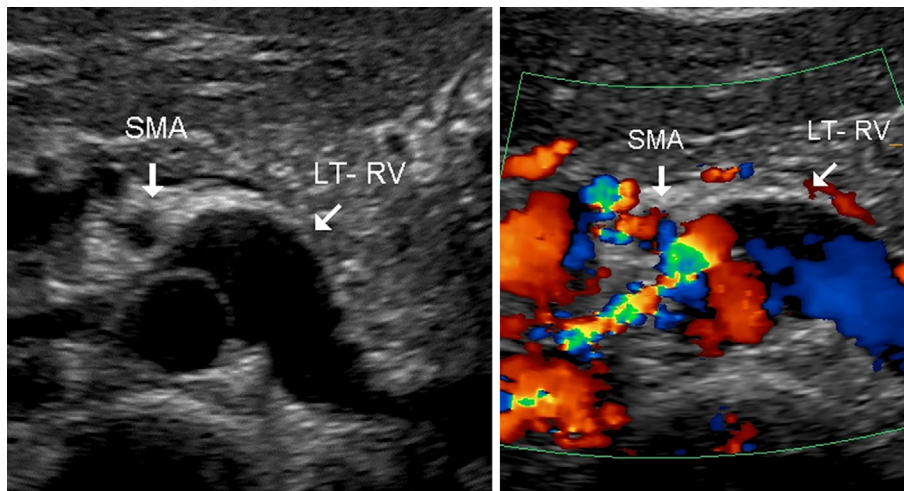


Figure 2. Renal vein ultrasonography. A b-mode ultrasound image (left panel) and a color Doppler image (right panel) of abdominal ultrasonography.



Figure 3. Enhanced computed tomography. An enhanced computed tomography image. The arrow shows the entrapment site of the left renal vein, which was distally dilated.

was severe, so renal vein stenting for NCS was considered; accordingly, renal venous ultrasonography was performed. Her renal vein was stenotic at 1.2 mm at the entrapment site but 11.4 mm at the renal hilum. The venous flow was accelerated at 200 cm/s at the entrapment site but was 16 cm/s at the renal hilum.

To confirm NCS, renal vein angiography was performed (Fig. 4). The existence of a pressure gradient was documented, with a left renal vein pressure of 14 mmHg and inferior vena cava pressure of 9 mmHg. Dilatation of the left ovarian vein as a collateral was also documented. Therefore, she was diagnosed with NCS. Her proteinuria was interpreted to be a result of the TBMD. No drugs were prescribed, and her degree of proteinuria was assessed at her regular visits. For the flank pain, she was instructed to avoid prolonged standing and lose more weight.

Discussion

We herein report a case of coexisting TBMD and NCS. TBMD and NCS are both common but are frequently missed. No report has described the coexistence of TBMD

and NCS with pathologic and radiographic confirmation; however, cases with the coexistence of TBMD and NCS are considered to exist and may merely be overlooked because of the morbidity of these two diseases. Both diseases cause flank pain and hematuria (1, 2), which complicate the diagnosis of one disease after the diagnosis of the other. Therefore, clues supporting the accurate diagnosis of hematuria and flank pain should not be overlooked; in this case, a clue to the presence of TBMD was the family history, and a clue to the presence of NCS was the exacerbated flank pain after prolonged standing.

TBMD is common and may affect approximately 1% of the population (3). It is frequently caused by mutations in the *Col4A3/4A4* gene (4). Over 90% of patients with TBMD develop hematuria (3); however, the incidence of flank pain in TBMD has not yet been determined. Recently, the renal prognosis of TBMD was revealed to be worse than previously thought, since over 20% of the patients need renal replacement therapy by 60 years of age (5). NCS is also common. In a report that investigated the morbidity associated with NCS using computed tomography, left renal vein entrapment between the abdominal aorta and superior mesenteric artery was detected in 4.1% of patients who underwent computed tomography. Given this frequency, asymptomatic left renal vein entrapment may also be present.

A low body mass index is known to be correlated with NCS morbidity (6). Doppler ultrasonography is recommended as the first diagnostic test in patients suspected of having NCS. Although Doppler ultrasonography reportedly has a high sensitivity and specificity for NCS, there are no established diagnostic criteria. An approximation and/or a sharpened angle between the abdominal aorta and superior mesenteric artery, an increased ratio of the renal hilum diameter to the aortomesenteric segment diameter, and an increased ratio of the blood velocity in the aortomesenteric segment to that in the renal hilum are proposed as useful indices (7-9). The diameter ratio and velocity ratio in the present patient were 12.5 and 9.5, respectively, both of which

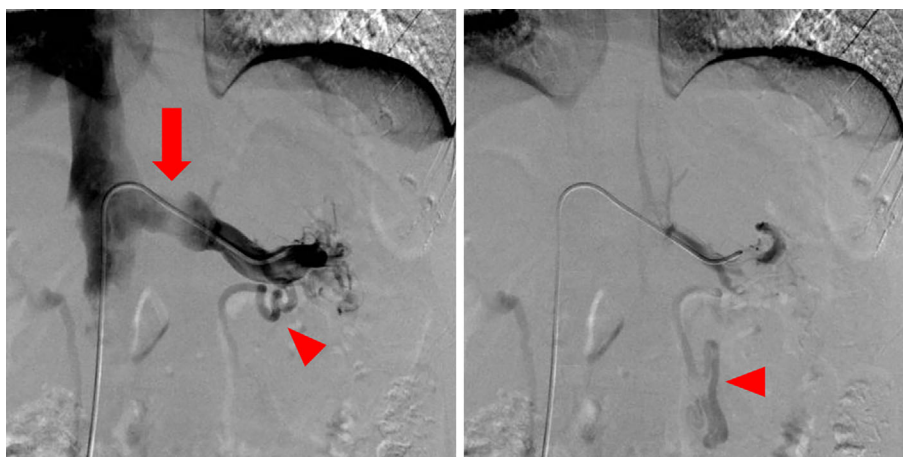


Figure 4. Renal vein angiography. An early-phase (left panel) and a late-phase image of renal venography are shown. The arrow indicates the entrapment site of the renal vein, and the arrowheads indicate the dilated left ovarian vein.

far exceed the ratios proposed for the diagnosis of NCS (5.0 for both parameters).

However, renal venography remains the gold standard for an NCS diagnosis. If the renal venous pressure is greater than the inferior vena cava pressure, with a cut-off of 3 mmHg, the pressure gradient is determined to be positive (2). Dilatation of the left ovarian (spermatic) vein is also evidence for left renal vein hypertension. In the present case, both the pressure gradient and dilatation of the left ovarian vein were documented, so NCS was diagnosed.

However, as renal venography is an invasive test, its indication should be limited. Intervention for NCS includes renal vein stenting and autotransplantation. Owing to the invasiveness of both procedures, advanced renal venography is needed. Therefore, renal venography may be indicated when these procedures are being considered. Severe manifestations, such as massive hematuria, which causes anemia or severe flank pain, are also indications. In the present case, the patient's severe flank pain was the indication for renal venography. If the flank pain remains severe after the avoidance of prolonged standing and further weight loss, renal vein stenting can be considered.

We performed a renal biopsy on her left side because we were unaware of the existence of NCS at the time of the biopsy. No evidence has proven that a left renal biopsy increases the risk of complication in cases with coexistence of NCS. The glomeruli of her left kidney were shown to be slightly collapsed, which might have been related to the glomerular hypoperfusion in NCS, as an elevated renal vein pressure led to a reduced renal artery blood flow and reduced glomerular filtration rate in an animal experiment in pigs (10). In that experiment, the animals in the renal vein hypertension group displayed more urinary protein than the sham operation group. The level of proteinuria in the present case was higher than that in typical cases of TBMD; while,

this finding may have been induced by TBMD alone, as heavy proteinuria is occasionally observed in TBMD (11), the possibility that NCS affects the level of proteinuria cannot be ruled out.

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

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