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An Unusual Case of Proteinuria in a Kidney Donor

Anju Yadav[1], Warren Maley[2] and Pooja Singh[1]

[1]Division of Nephrology, Department of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; and
[2]Division of Transplantation, Department of Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Correspondence: Anju Yadav, 833 Chestnut Street, Suite 700, Philadelphia, Pennsylvania 19107, USA. E-mail: anju.yadav@jefferson.edu

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INTRODUCTION

Urine protein excretion is a prerequisite test for evaluation of living kidney donor candidates. According to Kidney Disease: Improving Global Outcomes (KDIGO) living kidney donor guidelines, initial evaluation of donor albuminuria (screening) should be performed using random urine albumin-to-creatinine ratio (ACR).[1] Donor albuminuria should be confirmed using albumin excretion rate (AER, mg/d) in a timed urine specimen. Urine AER $<$30 mg/d is considered an acceptable level for donation.

CASE PRESENTATION

We present the case of a 41-year-old Caucasian woman, who was evaluated for kidney donation to her husband with end-stage renal disease. She had no past medical history. There was no history of urinary tract infection or kidney stones. She did not use nonsteroidal anti-inflammatory drugs, herbal medications, or any protein supplements. Surgical history was significant for augmentation mammoplasty. Family history was significant only for mother with breast cancer. She had never smoked and only drank alcohol socially on rare occasions. She was thin in build, normotensive, and had a body mass index of 22.3 kg/m^2. She followed a regular exercise regimen.

During the evaluation, she had no microalbuminuria on a spot albumin/creatinine ratio but had persistent $>$300 mg proteinuria in multiple 24-hour urine collections (Table 1). Split urine collection revealed the orthostatic nature of this proteinuria with supine proteinuria of 50 mg in 8 hours and standing proteinuria of 240 mg in 16 hours. Further evaluation for proteinuria included an antinuclear antibody (ANA) panel, which showed a speckled pattern with a low 1:40 titer with normal complement levels, and serum protein electrophoresis (SPEP) was negative for monoclonal protein spike or immunofixation. No hematuria was noted on routine urinanalysis. Renal ultrasound showed a normal-sized kidney for the patient's body mass index, which had no hydronephrosis, stones, or masses and which had normal echogenicity.

Computed tomography (CT) of the abdomen and pelvis, with and without contrast, revealed that the left renal vein had a marked change in caliber as it passed beneath the superior mesenteric artery, from 13 mm to 3 mm. There was a collateral vein extending posteriorly from the proximal vein, likely draining to the paravertebral veins. There was a single, widely patent renal artery to each kidney, with no early branching on either side. There was a single renal vein on either side (Figure 1).

The anatomic findings were believed to be a reasonable explanation for orthostatic proteinuria, and, after detailed discussion with the patient and discussion in our multidisciplinary team, she was cleared for living kidney donation. She underwent left donor nephrectomy via a laparoscopic approach, with no complications. Ten months after donation, a repeat 24-hour urine protein assessment showed complete resolution of proteinuria ($<$34 mg/24 h, 1 month after donation), acceptable renal function with a solitary kidney, and serum creatinine of 1.0 mg/dl. Currently, 3 years after donation, the patient's spot urine protein-to-creatinine ratio is $<$100 mg/g.

DISCUSSION

Persistent proteinuria is considered to be a contraindication to kidney donation.[2] A 2007 survey of practices by transplantation programs in the United States reported that 36% used protein excretion rates $>$150 mg/d as a

Table 1. Laboratory work

Laboratory tests	Laboratory values
Hemoglobin/hematocrit, mg/dl, n (%)	12.7 (37.5)
Platelet, B/L	263
White blood cells, B/L	4.6
Glucose, mg/dl	104
Blood urea nitrogen, mg/dl	15
Creatinine, mg/dl	0.6
Estimated glomerular filtration rate, ml/min per 1.73 m^2 body surface area	113
Liver function tests, coagulation profile	Within normal limits
Lipid panel	Within normal limits
Blood group	O+
HIV/toxoplasmosis/EBV PCR/CMV PCR	Negative
Hepatitis-B PCR/hepatitis-C PCR/QuantiFERON gold	Negative
Urine albumin/creatinine ratio, mg/g	<4
Body mass index, kg/m^2	22.3

24-h Urine studies

Timeline	24-h creatinine clearance (ml/min)	Protein/24 h
2 mo before donation	105	Protein 317 mg/24 h
1 mo before donation	108	Protein 350 mg/24 h
3 wk before donation		Orthostatic split proteinuria: Supine: 50 mg/8 h Standing: 240 mg/16 h
1 yr after donation		<34 mg/24 h; <4 mg/dl

CMV, cytomegalovirus; EBV, Epstein–Barr virus; PCR, polymerase chain reaction.

threshold for donor exclusion (unless proteinuria is postural), whereas 44% reported exclusion thresholds of 300 mg/d or higher.[1,3]

Nutcracker syndrome (NCS), or left renal vein entrapment syndrome, which is characterized by compression of the LRV between the superior mesenteric artery (SMA) and abdominal aorta, was first described in 1950 by El-Sadr and Mina.[4,5] Following this, Chait *et al.*[6] described the abdominal aorta and SMA as the 2 arms of a "nutcracker" that can potentially compress the LRV. This description prompted

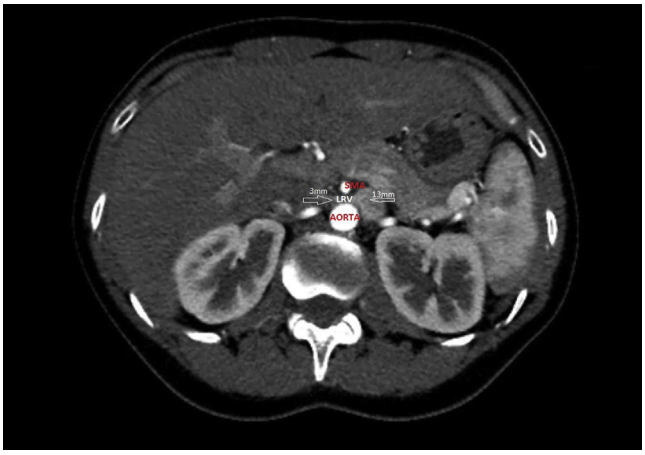

Figure 1. Computed tomogram of the abdomen, showing a change in the caliber of the left renal vein (LRV) as it passes between the superior mesenteric artery (SMA) and aorta.

Table 2. Clinical manifestations of nutcracker syndrome[2]

Symptom	Comment
Asymptomatic microhematuria	Present in 18% of cases
Severe pelvic congestion	Collateral veins may be evident on pelvic and abdominal Doppler ultrasound or venography
Overt hematuria	Attributed to rupture of thin-walled varices, due to elevated venous pressure into the collecting system; cystoscopy may identify a left ureteral origin
Abdominal or flank pain	Occasionally radiating to posteromedial thigh or buttocks
Varicocele	Left side; affects 9.5% of men
Orthostatic proteinuria	14% of Cases
Orthostatic intolerance	
Chronic fatigue syndrome	Due to high left renal vein–inferior vena cava, inferior vena cava pressure gradients; symptoms correlated positively with high peak velocity ratios measured by Doppler ultrasound

Belgian physician De Schepper to name this phenomenon as nutcracker syndrome.

Nutcracker syndrome refers to clinical manifestations related to the nutcracker phenomenon. Although it may be associated with substantial morbidity, the diagnosis of NCS is often difficult and delayed unless prompt imaging studies are obtained.[3]

Usually symptomatic patients present in second or third decade of life and a second peak in seen in middle aged women. The clinical manifestations of NCS are more prominent in the upright in comparison to supine position because of the visceral proptosis and changing aorto-mesenteric angle (i.e., the angle between the aorta and superior mesenteric artery). Physical activity, position, lower body mass index, weight loss, multiparity, and pregnancy can all aggravate symptoms of NCS (Table 2).

Most common clinical signs on presentation, such as proteinuria, hematuria, pain, pelvic varicosities, varicoceles, and pelvic congestion syndrome, should raise suspicion for the diagnosis.[7] The severity of clinical symptoms varies depending on the stages of pathological process. The evaluation and management plan need to be customized for the best patient outcomes. Combined NCS and Dumbar syndrome (also known as median arcuate ligament syndrome) have been reported.[8] Spontaneous resolution of the nutcracker phenomenon has been described in children after some years of persistence and may be due to changes in anatomic proportions associated with growth.

The primary diagnostic tests should be careful physical examination and elicitation of history. For hematuria and proteinuria, diagnostic methods include blood examinations, urinalysis, urine culture, cytology, ureteroscopy, and imaging (renal angiography, computed tomographic angiography, digital subtraction angiography, standard magnetic resonance imaging, and magnetic resonance angiography). In some cases, renal biopsy precedes the final diagnosis of NCS.

A computed tomographic angiogram is the imaging method of choice to diagnose NCP. However, multiphase computed tomographic urography has the ability to reveal other causes of hematuria, such as renal or urothelial tumors and arteriovenous malformation. It can demonstrate delayed nephrograms in patients with NCS, can clarify spatial relations between vessels, and is almost always required before surgical interventions to exclude other causes. Doppler ultrasound is also a helpful noninvasive modality and can be used if NCS is suspected clinically or if a large LRV diameter ratio is noted on plain ultrasound. Peak velocities are highly variable, depending on the position of the patient, and thus the peak velocity ratio may be more predictive.

Treatment of NCS is based on severity of symptoms and their expected reversibility, and the presence of comorbid conditions. Conservative treatment is recommended for mild hematuria. For patients younger than 18 years, a conservative approach for at least 2 years is recommended, because as many as 75% of the patients will have complete resolution of hematuria.[4] Angiotensin converting enzyme inhibitors may be helpful in improving orthostatic proteinuria in patient with NCS,[4] but there is lack of consensus on this approach.

Correlation between imaging evidence of LRV compression and clinical symptoms remains challenging, and therefore intervention should be considered only when symptoms are severe or persistent, including severe unrelenting pain, severe hematuria, renal insufficiency, and failure to respond to conservative treatment after 2 years.[4] Most interventions aim to decrease LRV hypertension, but others are directed against pelvic venous congestion. Operative surgical approaches have been used, including medical nephropexy with excision of renal varicosities, LRV bypass, LRV transposition, superior mesenteric artery transposition, renal to inferior vena cava shunt, renal autotransplantation,[9] gonadal-caval bypass, or nephrectomy for persistent hematuria.

Balloon-expandable and self-expanding stents have been used with anticoagulation for 2 to 3 months after the procedure.[4] Some patients are successfully managed with aspirin or clopidogrel without long-term anticoagulation. There is a paucity of long-term follow-up data on NCS.

Our patient had orthostatic proteinuria without other symptoms. Serology laboratory workup was nonrevealing. Imaging with computed tomographic angiography revealed nutcracker phenomenon. After donor nephrectomy, proteinuria resolved (3 years at the time of writing), and hence donor nephrectomy was curative in this case. The recipient's creatinine levels after 2 years post-transplantation have ranged between 1.1 and 1.3 mg/dl, with urine protein-to-creatinine ratio of 100 to 200 mg/g. Key learning points are enlisted in Table 3.

Table 3. Teaching points

Proteinuria assessment in a potential donor should include testing for orthostatic nature of proteinuria.
A potential living donor should not be ruled out automatically. If proteinuria has no obvious causes (serology, body mass index, etc.) and the donor wants to pursue donation, further contrast imaging and, in selected cases, a renal biopsy can be considered.
Nutcracker physiology is due to compression of the left renal vein between the superior mesenteric artery and inferior vena cava and has a wide range of presenting symptoms.
Management of nutcracker syndrome requires a multidisciplinary team approach for the best patient outcomes.

This case presentation demonstrates a rare but challenging case of NS in a potential living donor. Our donor had orthostatic presentation, and donor nephrectomy was curative. The recipient had excellent renal allograft function with no microalbuminuria during almost 3 years of follow-up. In summary, NCS is associated with reversible proteinuria, and this finding alone should not automatically rule out a kidney donor.

DISCLOSURE

All the authors declared no competing interests.

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