Interventional Management of Renal Vascular Origin Hematuria

Gregory J. Dubel, M.D.,¹ and Gregory M. Soares, M.D.¹

ABSTRACT

Several renal vascular pathological processes have been associated with hematuria. These include renal artery aneurysm (RAA), fibromuscular dysplasia (FMD), renal nutcracker syndrome (RNS), renal arteriovenous malformation, renal vasculitis, and renal artery or vein thrombosis. We present an unusual case of hematuria in a patient eventually diagnosed with RAA, FMD, and RNS. Percutaneous therapy, including endovascular coiling, percutaneous transluminal angioplasty, and stent placement were used to address the underlying pathology. The differential diagnosis, pathophysiology, and surgical and interventional management of these renal vascular disorders are reviewed.

KEYWORDS: Hematuria, fibromuscular dysplasia, nutcracker syndrome, renal artery aneurysm, vasculitis, coil, angioplasty, stent

Objectives: Upon completion of this article, the reader should understand the pathophysiology, natural history, and interventional and surgical treatment options for renal artery aneurysms, fibromuscular dysplasia, and renal nutcracker syndrome.

Accreditation: Tufts University School of Medicine (TUSM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit: TUSM designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The differential diagnosis for hematuria is extensive and includes nephrolithiasis, infections of the genitourinary tract, primary kidney disorders such as glomerulonephritis, bleeding disorders (hemophilia, platelet dysfunction or deficiency), renal trauma, and medications. One of the most feared causes of hematuria is malignancy, such as transitional cell or renal cell carcinoma. Although less common, renal vascular pathology may also result in hematuria. Renal artery aneurysm (RAA),^{1,2} fibromuscular dysplasia (FMD),³ and renal nutcracker syndrome (RNS)⁴ have all been reported in association with hematuria. The following case report details an unusual case combining these renal vascular pathological processes and serves as a paradigm for

discussion on the evaluation and management of these relatively uncommon disorders.

CASE REPORT

A 45-year-old woman was referred by her family physician for evaluation of gross hematuria of 1 week duration. Past medical history was significant for mild asthma, depression, mild intermittent hand swelling, low back pain, and bilateral knee arthritis with prior arthroscopy. She reported intermittent sinus infections. Her past surgical history included prior L4-L5 laminectomy and bilateral knee surgery. The family physician had excluded urinary tract infection by urinalysis and

¹Department of Diagnostic Imaging, Brown University Medical School, Providence, Rhode Island.

Address for correspondence and reprint requests: Gregory J. Dubel, M.D., Division of Interventional Radiology, Rhode Island Hospital, 593 Eddy Street, 3rd Floor Main Building, Providence, RI 02903.

Case-Based Interventional Radiology; Guest Editors, Ron C.

Gaba, M.D., Derek L. West, M.D., James T. Bui, M.D., Charles A. Owens, M.D.

Semin Intervent Radiol 2007;24:124-129. Copyright © 2007 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI 10.1055/s-2007-971201. ISSN 0739-9529.

Figure 1 (A) Initial selective right renal arteriogram documents 18-mm right renal artery aneurysm (asterisk) as well as beading of renal artery (arrow) suggestive of fibromuscular dysplasia. Note two vessels arising from aneurysm near the neck (arrowheads). (B) Arteriogram documents successful exclusion of aneurysm using detachable 0.018-inch coils. Note some compromise of flow to two vessels arising from aneurysm (arrowheads).

gram stain and culture. Laboratory work had revealed a normal complete blood count and platelet count. Urine was negative for protein. Cystoscopy was negative. A gadolinium-enhanced magnetic resonance (MR) angiogram was performed that suggested a right renal artery aneurysm and questioned mild right renal artery stenosis. After consultation with an interventional radiologist, the patient was scheduled for catheter angiography and potential intervention.

Initial aortogram confirmed a 1.6-cm right renal artery aneurysm, as well as beading of both main renal arteries typical of FMD. The right renal artery was selectively catheterized (Fig. 1A) with a 5F Cobra catheter (Cook, Bloomington, IN), and a Renegade Hi-Flo microcatheter (Boston Scientific, Natick, MA) was placed within the aneurysm. The aneurysm was then packed using Guglielmi Detachable Coils (GDCs; Target/Boston Scientific, Natick, MA), as well as a Vortex coil at the base (Target/Boston Scientific, Natick, MA). Post-coiling arteriogram confirmed exclusion of the aneurysm, with some pruning of peripheral vessels in the midportion of the kidney and sluggish antegrade flow to the lower pole branches arising from the aneurysm (Fig. 1B).

Following the aneurysm coiling, the patient had reduction in hematuria; however over a period of 6 weeks developed hypertension that was difficult to control. The patient returned for repeat arteriography to determine whether progressive FMD or vessel narrowing and flow impairment adjacent to the GDC mass had resulted in renovascular hypertension. Nonselective arteriography

revealed continued exclusion of the RAA, persistent findings of bilateral FMD, and interval thrombosis of the previously sluggish lower pole branches (Fig. 2A). Significantly, late venous phase images showed frank reflux into the left gonadal vein and minimal antegrade flow from the left renal vein into the inferior vena cava (IVC) suggestive of RNS (Fig. 2B). Percutaneous transluminal angioplasty (PTA) of both the right main and right upper pole and left main renal arteries was successfully performed, with reduction in amount of beading. Over the ensuing weeks the patient's hypertension improved significantly, and she was off all blood pressure medications except lisinopril, 20 mg daily. At this time she also complained of left flank pain. Given high suspicion of a RNS based on the angiogram, the patient returned for renal venography and potential intervention. Left selective renal venography was performed confirmed frank reflux into the left gonadal vein, filling of ureteric and lumbar collaterals, and compromised left renal vein outflow to the IVC (Fig. 3A). The mean gradient between the left renal vein and the IVC was 6 mm Hg. A 10 × 38 mm Express stent (Boston Scientific, Natick, MA) was successfully deployed across the stenosis (Fig. 3B), with a poststent gradient of 0 to 1 mm Hg. The patient's hematuria and left flank pain resolved. She has remained hematuria and pain free for 18 months.

DISCUSSION

Hematuria, which may be microscopic or macroscopic, is a common medical problem, occurring in up to 18% of

Figure 2 (A) Early aortogram images document successful exclusion of aneurysm (arrowhead) and beading of main renal artery (arrow) and segmental branches typical of fibromuscular dysplasia. (B) Delayed (venous phase) image from aortic injection shows venous congestion and retrograde filling of left gonadal vein (arrows) with minimal opacification of inferior vena cava (arrowheads).

the asymptomatic individuals on screening dipstick testing.⁵ A positive urine dipstick test must always be confirmed by examining urinary sediment to exclude myoglobinuria, which is not reliably differentiated by dipstick testing. The American Urological Association (AUA) defines clinically significant microscopic hematuria as three or more red blood cells per high power field on microscopic evaluation of urinary sediment from two

of three properly collected urinalysis specimens.⁵ Although microscopic hematuria may be benign, macroscopic hematuria and hematuria associated with proteinuria are generally evaluated aggressively.

The recommended evaluation of patients with hematuria follows a logical progression that includes a complete history and physical examination, clean catch urinalysis with gram stain and culture if pyuria or

Figure 3 (A) Left renal venogram documents dilated, refluxing gonadal vein, filling of periureteric collateral vessels, and nonopacification of inferior vena cava (IVC). (B) Left renal venogram following stent placement demonstrates near complete resolution of gonadal vein reflux and spontaneous flow in IVC. Poststenting pressure gradient was 0 to 1 mm Hg.

bacteruria are present, complete blood count with platelet count, and coagulation tests. Special attention should be directed toward medications that might cause hematuria (such as nonsteroidal anti-inflammatory drugs, statins, cocaine, methadone, and ethanol) and trauma as minimal as running, which may cause hematuria in some patients.⁶ When proteinuria is present with hematuria, there is a high likelihood of glomerular disease, and kidney biopsy may be required. Should this initial evaluation fail to reveal the source of the hematuria, cystoscopy and retrograde urography and computed tomography (CT) or CT urography may be warranted. The CT examination is critical to exclude nephrolithiasis, renal masses (such as renal cell carcinoma or transitional cell carcinoma), large vascular malformations (arteriovenous malformation [AVM] or arteriovenous fistula [AVF]), and to detail unusual anatomy (retroaortic renal vein, ureteric duplication, horseshoe kidney). MR angiography may be used when renal vascular pathology is suspected or if the CT is unrevealing. When these tests fail to reveal the cause of the hematuria, catheter-based renal angiography may be useful to localize small vascular malformations (AVM or AVF), to evaluate dysplastic vessels, and to seek evidence of small vessel vasculitis. Renal venography is useful, as was demonstrated in this case, in evaluating for RNS and obtaining pressure measurements. Catheter-based angiographic assessment is also indicated when cross-sectional studies suggest pathology amenable to percutaneous intervention.

The "renal nutcracker" was first coined by Grant, who stated "the left renal vein as it lies between the aorta and the superior mesenteric artery resembles a nut between the jaws of a nutcracker."⁷ Renal nutcracker physiology exists in many patients with asymptomatic dilation of the left renal vein (LRV), having been described as a normal variant occurring in up to 50 to 70% of the population.⁸ In some patients, the increased venous pressure promotes the development of collateral vessels in the renal pelvis and direct channels of communication between extremely thin-walled venous sinuses and adjacent calyces, resulting in hematuria.⁹ RNS refers to a constellation of signs and symptoms seen in association with renal vein obstruction or compression that includes hematuria, left flank pain, orthostatic proteinuria,¹⁰ pediatric chronic fatigue syndrome,¹¹ varicocele in males, and pelvic congestion syndrome in females. De Schepper first detailed the venographic findings of RNS in 1972 in a 16-year-old boy with hematuria.¹² Venographic findings include dilation of the LRV, formation of periureteric, perirenal, and lumbar collaterals, delayed or nonfilling of the IVC, and reflux in the gonadal vein. Although there is wide variation in the pressure gradient between the IVC and the LRV, Nishimura and others have suggested that a mean gradient of > 3 mm Hg is abnormal.¹³⁻¹⁵ Cheon et

al used renal vein Doppler ultrasound to screen patients for RNS.¹³ Using peak velocity (PV) in the mesoaortic segment of > 93 cm per sec and PV ratios between the hilar and the mesoaortic segments of the LRV of > 4.7 yielded a sensitivity of 100%, specificity of 85%, and accuracy of 89% in diagnosing RNS.

There is no consensus on the best treatment for RNS in patients with incapacitating pain or hematuria. Multiple surgical treatments have been used with varying degrees of success, including treatments as radical as superior mesenteric artery (SMA) transposition and nephrectomy.¹⁶ Autotransplantation and renal vein transposition offer good outcomes with relatively less morbidity than SMA transposition, which has fallen out of favor. In one series, Hohenfellner et al described resolution of hematuria in seven of eight patients treated with left renal vein transposition.¹⁷ Complications occurred in four, including DVT, paralytic ileus, hematoma necessitating evacuation, and adhesions requiring surgery. A single patient had persistent hematuria despite normalization of the renocaval pressure gradient. This is thought to be related to well-developed changes in the renal vascular architecture that may be irreversible at the time of the procedure.¹⁶⁻¹⁸ Although surgical procedures can be effective, the lack of 100% cure rates coupled with complications make minimally invasive treatments attractive.

Minimally invasive management treatment options of RNS have included conservative "watchful waiting,"¹⁹ ureteroscopic chemical cauterization using silver nitrate,^{20,21} venoplasty alone,²² and primary stenting.²³ The watchful waiting approach is particularly applicable to young slender individuals where the anatomical factors causing left renal vein compression may change as patients increase in height, weight, or both.^{19,24} Although minimally invasive, the instillation of silver nitrate has only one report of success²¹ and one failure²⁰ so that no conclusion can be reached regarding its safety or efficacy. Similarly, venoplasty alone has been used rarely to treat RNS.²² Anatomically, venoplasty could be useful in cases where there has been fibrosis of the left renal vein; however, by itself, it is unlikely to improve most cases where there is physical compression of the vein by the abnormally small space between the SMA and the aorta.

Stenting for RNS was first described by Neste in 1996²³ and has been used successfully by others.^{20,25-27} Improvement in pain and/or hematuria has been reported in 13 of 14 published cases. Both balloon-expandable and self-expanding stents have been used successfully. Although delayed stent migration has been reported with self-expanding stents,^{25,28} the phenomenon may be related to the use of inappropriately sized stents. Most patients have been placed on anti-coagulation or antiplatelet medications for 3 to 6 months following the procedure, and thus far stent thrombosis

has not been problematic. The treatment appears highly effective with significantly lower complication rates compared with surgery.

The coexistence of RNS, FMD, and RAA in this patient makes the etiology of the hematuria particularly intriguing. Because cystoscopy failed to lateralize the side of bleeding to right or left, it is impossible to know the exact contribution of each process (RAA on the right, RNS on the left, or bilateral FMD). Renal artery aneurysms are present in <1% of the population.²⁹ Unlike aneurysms elsewhere in the body, these aneurysms appear to be more commonly associated with FMD than with atherosclerotic disease.³⁰ Rare causes of RAA include vasculitides (systemic lupus erythematosus [SLE], polyarteritis nodosa, Behçet's disease, Takayasu arteritis), collagen vascular disorders such as Ehlers-Danlos, and prior trauma (biopsy).

Most RAAs are discovered incidentally in asymptomatic patients during MR imaging and CT examinations performed for other reasons; however, a small percentage present with pain or hematuria, as do a small number of patients with FMD. Also similar to FMD, some patients present with hypertension, renal artery dissection or occlusion, or segmental renal infarctions. Treatment of RAA is generally performed for symptomatic aneurysms or those > 2 cm, although reports exist of rupture in those < 2 cm. Hormonal changes during pregnancy are thought to predispose patients to rupture such that repair may be suggested in female patients planning future pregnancy with RAA measuring < 2 cm. The largest RAA surgical series includes 126 patients and reports 0% mortality with intended and unintended nephrectomy rates of 21% and 6%.³⁰ Significant complications included single cases of retroperitoneal hematoma, deep venous thrombosis, pneumonia, graft thrombosis, and renal failure. Renal artery PTA > 1 month postsurgery was required in four patients. This series suggests that surgery can be performed safely in experienced centers for patients with complex aneurysms, albeit with a significant risk of nephrectomy. An increasing body of evidence indicates that endovascular coiling can be performed in selected patients with favorable anatomy using various types of coils.³¹⁻³³ In patients with complex anatomy or wide necks, detachable coils (GDC) and balloon-remodeling techniques have proven useful in preserving flow to uninvolved vessels.

The treatment of choice for hypertensive patients with FMD without aneurysm is PTA.^{34,35} Technical success rates are generally $\geq 95\%$ with improvement or cure in hypertension in 90% and improvement in renal function in 95 to 100% of those with impaired function. Restenosis occurs in 10 to 23% (1 to 10 years) and can generally be easily redilated.

Patients with vasculitides may have renal vascular pathology detected on screening imaging or may present in extremis after renal artery or aneurysm rupture. The

mainstay of treatment for stable patients is directed at their underlying disorder and often includes steroids or other immunosuppressive therapy. Coil embolization has been used to treat ruptures.^{36,37} Limited experience with PTA to treat symptomatic stenoses resulting in hypertension or azotemia suggests it may be useful in carefully selected patients.³⁸ Renal vein thrombosis (RVT), which occurs in up to 10% of those with nephrotic syndrome, may also be seen in association with Behçet's disease and SLE, and present with hematuria. Recent experience suggests that percutaneous pharmacomechanical thrombolysis can be effective in treating RVT with minimal complications and a high degree of success in improving renal function.³⁹

CONCLUSION

In summary, the etiology of hematuria comprises a complex differential diagnosis but is most often related to renal parenchymal disease or nephrolithiasis. Interventional radiologists should be familiar with the various disease states associated with hematuria and affecting the renal vasculature. These include RAA, FMD, RNS, RVT, trauma, and renal vasculitides. Catheter-based angiography continues to play important diagnostic and therapeutic roles in the management of many of these entities.

REFERENCES

1. El Kharras A, Salaheddine T, Aziz N, Jidal M, Chaouir S, Benameur M. A rare cause of hematuria: rupture of a renal artery aneurysm—a case report. *J Radiol* 2005;86:954–956
2. Romero-Teran O, Torres-Contreras LM, Mora-Fol JR, Andrade-Sepulveda VR, Baeza-Herrera C. Calcified renal artery aneurism and high blood pressure: a case report and review of the literature [in Spanish]. *Cir Cir* 2004;72:217–220
3. Barbey F, Matthieu C, Nseir G, Burnier M, Teta D. A young man with a renal colic. *J Intern Med* 2003;254:605–608
4. Shaper KR, Jackson JE, Williams G. The nutcracker syndrome: an uncommon cause of haematuria. *Br J Urol* 1994;74:144–146
5. Grossfeld GD, Litwin MS, Wolf JS, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy—part I: definition, detection, prevalence, and etiology. *Urology* 2001;57:599–603
6. Mazhari R, Kimmel PL. Hematuria: an algorithmic approach to finding the cause. *Cleve Clin J Med* 2002;69:870–876
7. Grant JCB. *Methods of Anatomy*. Baltimore: Williams & Wilkins; 1937:158
8. Buschi AJ, Harrison RB, Norman A, et al. Distended left renal vein: CT/sonographic normal variant. *AJR Am J Roentgenol* 1980;135:339–342
9. Macmahon HE, Latorraca R. Essential renal hematuria. *J Urol* 1954;71:667–676

10. Ekim M, Ozcakar ZB, Fitoz S, et al. The "nutcracker phenomenon" with orthostatic proteinuria: case reports. *Clin Nephrol* 2006;65:280-283
11. Takemura T, Iwasa H, Yamamoto S, et al. Clinical and radiological features in four adolescents with nutcracker syndrome. *Pediatr Nephrol* 2000;14:1002-1005
12. De Schepper A. "Nutcracker" phenomenon of the renal vein and venous pathology of the left kidney. *J Belge Radiol* 1972; 55:507-511
13. Cheon JE, Kim WS, Kim IO, et al. Nutcracker syndrome in children with gross haematuria: Doppler sonographic evaluation of the left renal vein. *Pediatr Radiol* 2006;36:682-686
14. Hohenfellner M, Steinbach F, Schultz-Lampel D, et al. The nutcracker syndrome: new aspects of pathophysiology, diagnosis and treatment. *J Urol* 1991;146:685-688
15. Nishimura Y, Fushiki M, Yoshida M, et al. Left renal vein hypertension in patients with left renal bleeding of unknown origin. *Radiology* 1986;160:663-667
16. Ahmed K, Sampath R, Khan MS. Current trends in the diagnosis and management of renal nutcracker syndrome: a review. *Eur J Vasc Endovasc Surg* 2006;31:410-416
17. Hohenfellner M, D'Elia G, Hampel C, Dahms S, Thuroff JW. Transposition of the left renal vein for treatment of the nutcracker phenomenon: long-term follow-up. *Urology* 2002;59:354-357
18. Rudloff U, Holmes RJ, Prem JT, Faust GR, Moldwin R, Siegel D. Mesoaortic compression of the left renal vein (nutcracker syndrome): case reports and review of the literature. *Ann Vasc Surg* 2006;20:120-129
19. Tanaka H, Waga S. Spontaneous remission of persistent severe hematuria in an adolescent with nutcracker syndrome: seven years' observation. *Clin Exp Nephrol* 2004;8:68-70
20. Segawa N, Azuma H, Iwamoto Y, et al. Expandable metallic stent placement for nutcracker phenomenon. *Urology* 1999;53:631-633
21. Yu G, Bo S. The nutcracker syndrome. *J Urol* 2003;169: 2293-2294
22. Oteki T, Nagase S, Hirayama A, et al. Nutcracker syndrome associated with severe anemia and mild proteinuria. *Clin Nephrol* 2004;62:62-65
23. Neste MG, Narasimham DL, Belcher KK. Endovascular stent placement as a treatment for renal venous hypertension. *J Vasc Interv Radiol* 1996;7:859-861
24. Shin JI, Park JM, Lee SM, et al. Factors affecting spontaneous resolution of hematuria in childhood nutcracker syndrome. *Pediatr Nephrol* 2005;20:609-613
25. Hartung O, Grisoli D, Boufi M, et al. Endovascular stenting in the treatment of pelvic vein congestion caused by nutcracker syndrome: lessons learned from the first five cases. *J Vasc Surg* 2005;42:275-280
26. Scultetus AH, Villavicencio JL, Gillespie DL. The nutcracker syndrome: its role in the pelvic venous disorders. *J Vasc Surg* 2001;34:812-819
27. Park YB, Lim SH, Ahn JH, et al. Nutcracker syndrome: intravascular stenting approach. *Nephrol Dial Transplant* 2000;15:99-101
28. Lin WQ, Huang HF, Li M, et al. Diagnosis and therapy of the nutcracker phenomenon: long-term follow-up. *Zhong-hua Wai Ke Za Zhi* 2003;41:889-892
29. Stanley JC, Rhodes EL, Gewertz BL, Chang CY, Walter JF, Fry WJ. Renal artery aneurysms: significance of macroaneurysms exclusive of dissections and fibrodysplastic mural dilations. *Arch Surg* 1975;110:1327-1333
30. Henke PK, Cardneau JD, Welling TH III, et al. Renal artery aneurysms: a 35-year clinical experience with 252 aneurysms in 168 patients. *Ann Surg* 2001;234:454-462
31. Ishizuka O, Takayama F, Sone S. Large renal aneurysm successfully treated by percutaneous embolization using detachable steel coils. *Int J Urol* 2006;13:993-994
32. Klein GE, Szolar DH, Breinl E, Raith J, Schreyer HH. Endovascular treatment of renal artery aneurysms with conventional non-detachable microcoils and Guglielmi detachable coils. *Br J Urol* 1997;79:852-860
33. Trocciola SM, Chaer RA, Lin SC, et al. Embolization of renal artery aneurysm and arteriovenous fistula: a case report. *Vasc Endovascular Surg* 2005;39:525-529
34. Birrer M, Do DD, Mahler F, Triller J, Baumgartner I. Treatment of renal artery fibromuscular dysplasia with balloon angioplasty: a prospective follow-up study. *Eur J Vasc Endovasc Surg* 2002;23:146-152
35. Tegtmeier CJ, Selby JB, Hartwell GD, Ayers C, Tegtmeier V. Results and complications of angioplasty in fibromuscular disease. *Circulation* 1991;83:I155-I161
36. Sueyoshi E, Sakamoto I, Hayashi N, et al. Ruptured renal artery aneurysm due to Behcet's disease. *Abdom Imaging* 1996;21:166-167
37. Planer D, Verstandig A, Chajek-Shaul T. Transcatheter embolization of renal artery aneurysm in Behcet's disease. *Vasc Med* 2001;6:109-112
38. Park JH, Han MC, Kim SH, Oh BH, Park YB, Seo JD. Takayasu arteritis: angiographic findings and results of angioplasty. *AJR Am J Roentgenol* 1989;153:1069-1074
39. Kim HS, Fine DM, Atta MG. Catheter-directed thrombectomy and thrombolysis for acute renal vein thrombosis. *J Vasc Interv Radiol* 2006;17:815-822