CLINICAL VIGNETTE

Urgent Renal Artery Stenting as Successful Treatment of Rapidly Progressive Anuric Renal Artery Stenosis in a Single-Kidney Patient

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Case Presentation

A 73-year-old male with a history of right renal cell carcinoma status post-nephrectomy and left atherosclerotic renal artery stenosis (ARAS) presented to the emergency department with 12 hours of left flank pain, mild malaise, and possible decreased urine output. He denied dysuria, fevers, chills, or nausea. He reported mild chronic intermittent urinary hesitancy, unchanged for years. Other medical history included hypertension, obesity, diet-controlled diabetes mellitus, benign prostatic hyperplasia, hyperlipidemia, and coronary artery disease with non-ST-elevation myocardial infarction (NSTEMI) treated with drug-eluting stents nine months prior. Medications on admission included: losartan, metoprolol, finasteride, tamsulosin, clopidogrel, aspirin, and fish oil. He reported statin intolerance.

The patient was hypertensive to 180/80 mm Hg on presentation but was otherwise stable. Physical exam was pertinent for moderate L costovertebral angle tenderness and a R nephrectomy scar. The jugular vein was flat; there were no pulmonary crackles and no edema. Admission chemistry panel was remarkable for an increase in creatinine of 2.65 mg/dL, from a stable baseline value averaging 1.7 mg/dL every three months since his right nephrectomy 6 years earlier. Three months prior to admission, his longstanding losartan was increased from 50 mg to 100 mg daily. Urinalysis on admission showed moderate blood with 2 RBC per high-powered field and was negative for protein, bacteria, nitrites, leukocyte esterase, while urine sediment was bland. Creatine kinase was normal at 155 u/L. CBC was normal without leukocytosis. A kidney-stone-protocol non-contrast CT of the abdomen and pelvis confirmed an absent right kidney and demonstrated left kidney perinephric fat stranding with possible mild hydronephrosis but only identified a tiny 1 mm punctate nonobstructing calculus.

Due to the history of renal artery stenosis and the AKI, a renal ultrasound including vascular Doppler study showed no hydronephrosis and mild-to-moderate post-void residual urine. The Doppler was of poor quality but did demonstrate significantly elevated peak systolic velocity of blood flow through the left renal artery, estimated at 250 cm/s, likely an underestimate due to suboptimal ultrasound beam/flow velocity angle. A higher quality study from four months prior had shown similar results and included one focal velocity elevation in the left proximal main renal artery to 450 cm/s, consistent with severe stenosis.

Clinical Decision Making

The patient was admitted to the general medical service for work-up, monitoring, and treatment of his acute kidney injury (AKI) and left flank tenderness. Due to the residual urine detected in the bladder, the known BPH, ongoing symptoms, and the suggestion from CT of mild left hydronephrosis, tamsulosin dose was increased to 0.8 mg per day, and a Foley catheter was placed and maintained for close measurement of urine output. Therapeutically, the patient's ARB and aspirin were both held upon admission to reduce any ongoing renal insult. Hydralazine was titrated in place of the ARB to successfully decrease the blood pressure from the critically elevated range to normotension. The serum potassium level had been mildly elevated to 5.7 mmol/L on admission and successfully treated with kayexalate. Although the fractional excretion of sodium was calculated as 3% suggesting intrinsic AKI, a trial of IV hydration with 2 liters of normal saline under close monitoring was recommended by the nephrology service. Nephrology evaluation also included workup for rarer causes of intrinsic AKI, revealing normal complement levels, and negative test results for anti-GBM antibodies, ANCA, ANA, MPO, Hepatitis B, and Hepatitis C.

The patient's urine output declined, and he was oliguric by hospital day 2, while creatinine doubled to 4.7 mg/dL and serum bicarbonate level fell from 24 to 20 mmol/L. LDH to evaluate for possibility of kidney necrosis had uptrended from 177 U/L on admission to 201 U/L. A MAG-3 radioisotope renogram was recommended by the nephrology service on hospital day 2 to evaluate renal blood supply and function. It revealed moderately delayed blood flow to the kidney as well as no secretion of radiolabeled tracer into the bladder, suggesting both active renal artery stenosis and acute kidney injury.

The interventional radiology service was involved early in the patient's care. Initially, given concern for other differential diagnoses (obstructive uropathy from BPH, pyelonephritis, or the possibility of a radiolucent renal stone obstructing single-kidney urine output), there had been clinical equipoise on whether to move forward with endovascular renal artery stent

placement. However, the Foley catheterization had not helped maintain urine output, serial UAs were not suggestive of infection, and the patient's flank pain was dull and constant rather than the colicky pain that might be expected of a radiolucent stone missed by CT. These facts, along with the findings from the renal Doppler ultrasound, the MAG-3 study, the negative intrinsic AKI studies, and a lack of urine output after early fluid resuscitation, all led to consensus that the primary cause for the AKI was critical RAS with acute renal ischemia in the setting of pre-existing single-kidney RAS and the increased ARB dose.

Interventional possibilities including endovascular stent placement were discussed. Principal risk is of arterial contrast bolus directly on an injured single kidney with moderate likelihood of resultant contrast nephropathy requiring dialysis and unsure recovery. The vascular surgery service was thus consulted regarding an open direct revascularization of the single kidney via aorto-renal bypass. After consideration of the patient's other risk factors, including obesity and need for continuous clopidogrel (based on recent coronary stent) with high likelihood of further AKI from intraoperative hypotension or resultant volume shifts, it was decided that the surgical route had higher risk of complication than endovascular intervention. On hospital day 3, the patient had become anuric, and serum creatinine increased to 7 mg/dL. A multidisciplinary meeting involving the hospitalist, interventional radiologist, nephrologist, vascular surgeon, and urologist reviewed treatment options with the patient. The patient was in favor of endovascular intervention over expectant management, high likelihood of losing function of his sole kidney due to critical renal artery stenosis.

Resolution

The patient underwent successful placement of a left renal artery stent (5 x 19 mm Boston Scientific Express stent) with low dose diluted contrast, totaling only 12 mL. Initial angiography showed a severe left renal artery stenosis less than 1 cm from the ostium (Figure 1) with resolution of the stenosis upon stenting (Figure 2). Follow-up Doppler ultrasound evaluation confirmed no further evidence of physiologic renal artery stenosis and normal intrarenal resistive indices. The patient's flank pain and tenderness resolved within one day of stenting. He remained anuric with no improvement in serum creatinine for two days following the procedure and required one session of hemodialysis due to worsening acidosis. By post-procedural day 3, his urine output increased markedly, and he required three days of electrolyte repletion before discharge due to post-AKI-diuresis. His serum creatinine measurement gradually decreased to 1.97 mg/dL as an outpatient ten days after the procedure and was stable at 1.81 mg/dL three months later. The patient remains healthy, normotensive, dialysis-free, and suffered no long-term sequelae of his RAS, AKI, or stent placement in the ensuing months. His cardiologist has recommended continuing lifelong dual anti-platelet therapy due to his complex coronary and renal vascular disease. His nephrologist will periodically follow his ARAS for in-stent restenosis or further atherosclerotic lesions with Doppler US and is considering a closely-monitored and slow ARB re-challenge.

Discussion

Renal artery stenosis (RAS) is intraluminal narrowing of one or both renal arteries and represents an important cause of refractory hypertension as well as chronic ischemic nephropathy. RAS affects up to 7% of the American population over the age of 65.[1] It is generally detected during workup of refractory hypertension or kidney disease but can also be found incidentally during unrelated imaging or on autopsy.[2,3] Non-invasive renal duplex Doppler ultrasound is the most widely used tool to screen for RAS with the single measurement of peak systolic flow velocity through renal artery of greater than 200 cm/s showing a 85% sensitivity and 92% specificity for RAS at a commonly accepted 60% diameter stenosis angiographic threshold.[4] Computed tomographic angiography and magnetic resonance angiography have higher sensitivity and specificity for RAS than US, while renal artery catheterization with digital subtraction angiography remains the gold standard for diagnosis.[5] An estimated 10% minority of RAS cases are attributable to fibromuscular dysplasia (FMD), for which the archetypal adult patient is a younger female presenting with a paroxysmal hypertension. These cases usually demonstrate typical FMD pattern on angiogram with interspersed renal artery ectasia and stenosis and are generally amenable to effective treatment by renal artery balloon angioplasty.[6] A much smaller fraction of RAS cases is due to long-term sequelae of surgical and endovascular aortic interventions. The vast majority of RAS and principle topic of this discussion is atherosclerotic RAS, occurring most commonly near the renal artery ostium where blood flow is subject to the most turbulence.[7]

Development and progression of atherosclerotic renal artery stenosis (ARAS) shares common risk factors and correlates with other vascular diseases. Up to 20% of patients undergoing cardiac catheterization are incidentally found to have ARAS with stenosis greater than 50%, and both the presence and the severity of ARAS have been linked to cardiovascular mortality.[8] ARAS is the principal cause of ESRD requiring dialysis in up to 15% of dialysis patients over age 50 with ARAS-based dialysis patients manifesting worse long-term outcomes than most other renal disease groups.[9] The main mechanisms by which ARAS leads to ESRD include inducing chronic hypertension with hypertensive nephropathy and chronic ischemic nephropathy from direct limitation of blood flow.[10] The neurohormonal basis of chronic hypertensive nephropathy caused by ARAS is multifactorial in nature and described in depth elsewhere. For our patient, ischemic nephropathy dominated the clinical picture and occurred in an acute manner. His single-kidney physiology likely predisposed him to such a rapid progression of ischemic nephropathy with the pre-existing stenosis limiting afferent glomerular blood flow, while the ARB-mediated efferent vasodilation further critically decreased the GFR in a cycle that led to renal hypoperfusion and ischemia.

AKI due to RAS does not generally occur in patients with two functioning kidneys and unilateral ARAS likely due to compensatory glomerular filtration from the contralateral kidney. Acute ARAS has been described in single-kidney patients (or bilaterally significant ARAS patients who have

similar physiology to single-kidney ARAS) occasionally as manifesting with hypertensive crisis and flash pulmonary edema, sometimes amenable to urgent renal stent placement.[11,12] However, anuric acute ARAS is not common: a PubMed search of combinations of the terms "acute," "renal artery stenosis," "ischemic nephropathy," "kidney injury," "bilateral renal artery stenosis," and "single kidney" identified only a few case reports and one case series of acute ischemic nephropathy from severe ARAS (in absence of obstructive thrombus/embolus), the latter dating to the pre-stenting era. Roche and colleagues in 1993 described six patients presenting with acute anuric renal failure in absence of severe hypertension and the presence of ARAS. Four had a solitary kidney and the other two had kidney size disparity with ARAS of the kidney most relevant to overall GFR (the larger kidney). Four of their six patients opted to undergo acute open surgical renal artery bypass surgery and recovered renal function, while the other two declined surgery and continued on hemodialysis even a year later.[13] Since that time, increased availability of less-invasive endovascular renal artery stenting has led to frequent stenting of single kidney RAS or bilateral RAS for a variety of indications. We have found no other *acute* cases of single-kidney ARAS treated by stent.

Over the past 20 years, there has been much debate over the role of intervention for ARAS. Surgical revascularization had been done commonly through the early 1990's for patients with refractory hypertension and/or progression of ischemic nephropathy thought due to ARAS but was then largely supplanted by balloon angioplasty due to mounting evidence suggesting equal efficacy and less morbidity with the less invasive latter approach.[14] By 2000, large randomized, controlled trials demonstrated longer duration of renal artery patency in ARAS patients when angioplasty was followed by endovascular stent placement. Now, most patients selected for ARAS intervention receive stents.[15]

In parallel to these developments, medical therapies for atherosclerotic diseases also improved dramatically. Multiple retrospective analyses suggest that HMG-CoA reductase (statin) therapies aimed at decreasing cholesterol may also serve to dramatically reduce progression of ARAS and mortality in ARAS patients.[16,17] Furthermore though ACE inhibitors and ARBs decrease intraglomerular pressure (via out-of-proportion efferent arteriolar vasodilation) and can lead to severe impairment of GFR in a subset of ARAS patients, these medications are protective for the majority of such patients. A large recent single-center study found 92% of unilateral and 78% of bilateral ARAS patients could tolerate ARAS inhibition and that ARAS patients adherent to these medications demonstrated a 39% reduction in overall mortality compared with those assigned alternate anti-hypertensive drugs after controlling for confounders.[18] Thus, ACE inhibitors and ARBs are considered standard-of-care therapies in the treatment of ARAS, but titrations need to be carefully monitored with laboratory surveillance of creatinine within 3 to 5 days of drug titration, which was not performed in the patient of this report.

The impressive data regarding medications in ARAS begged the question of whether the optimal form of ARAS intervention, angioplasty with stent placement, would be superior to medical therapy with statin and carefully monitored ARAS blockade. While some early trials suggested superiority of endovascular procedures over medical therapy alone, the larger ASTRAL and STAR randomized control trials did not find significant difference in primary outcomes. These trials, however, had shortcomings including inclusion of some patients without observable hypertension, without CKD, and even some below the commonly accepted 60% threshold for stenosis.[19,20] The contemporary CORAL trial enrolled 947 participants, all of whom had >60% angiographic ARAS plus Stage 3 CKD or refractory hypertension. The ARAS cohort and the medical-management-only cohort had no differences in negative cardiovascular or renal outcomes after 43 months of follow up, with very few crossover events.[21] Although ACC/AHA guidelines have not yet been updated to reflect these data, the general consensus is that the best management for most ARAS is medical.

Despite this information, there are still scenarios for which stenting may be useful for ARAS patients, and careful patient selection will be an increasingly important.[22] A single center retrospective analysis of patients with "highest-risk" ARAS presentations, including flash pulmonary edema and very rapid decline in GFR, found revascularizing had 57% reduction in adverse cardiovascular events or death after a median 3.8 years follow-up. Revascularization in the "low risk group" did not make a significant difference.[23] Single kidney or bilaterally significant ARAS patients facing these high-risk situations putatively have even higher risk of losing all renal function and thus should also be considered for stenting in the acute renal failure setting.

Conclusion

This case demonstrates a few key points regarding atherosclerotic renal artery stenosis.

1) While prophylactic stenting for significant unilateral ARAS has been shown to confer no additional benefit, medical therapy (specifically statin and ACE inhibitor or ARB) is of utmost importance in preventing adverse events and delaying progression to dialysis in ARAS patients.

2) Serum creatinine should be reassessed within a few days of addition or uptitration of ACE/ARB in ARAS patients as an increase in serum creatinine > 30% is likely informative of bilateral significant RAS or "critical" RAS in the single-kidney population, necessitates ACE/ARB cessation, closer monitoring for AKI resolution, and consideration of interval stent placement if resolution does not ensue.

3) In cases where the majority of renal mass is affected by ARAS (including patients with a single functional kidney and those with bilaterally significant ARAS), early interventional management with endovascular stent should be considered if significant stenosis exists (>200 m/s flow on Doppler US, followed by confirmation of >60% diameter stenosis), especially if there is hypertension with flash pulmonary edema or acute decrease of GFR.

4) Though ARAS is more commonly associated with gradual CKD, anuric acute kidney injury may also occur from progression of ARAS in the setting of a single kidney and

might in some cases be accompanied by dull flank pain similar to that of embolic infarction.

5) In such cases, urgent renal artery stenosis intervention should be considered during the interdisciplinary workup for other causes AKI. Even for poor open-surgical candidates, a positive outcome with full renal recovery may still be attained in some candidates via timely endovascular stent placement.

Figures and Images

Figure 1. Pulse-wave Doppler ultrasound of the patient's left kidney on presentation, demonstrating flow acceleration through L renal artery to 248 cm/s^2, suggesting significant renal artery stenosis.

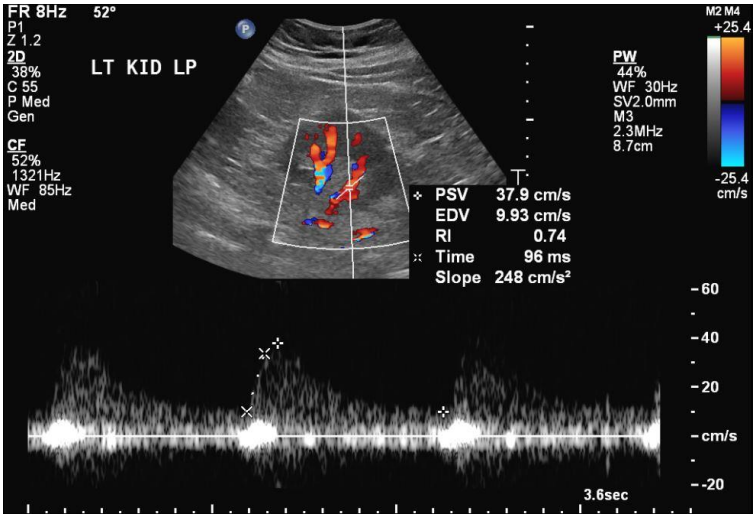
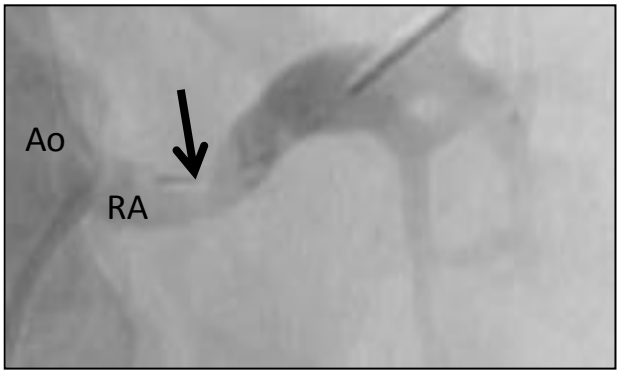
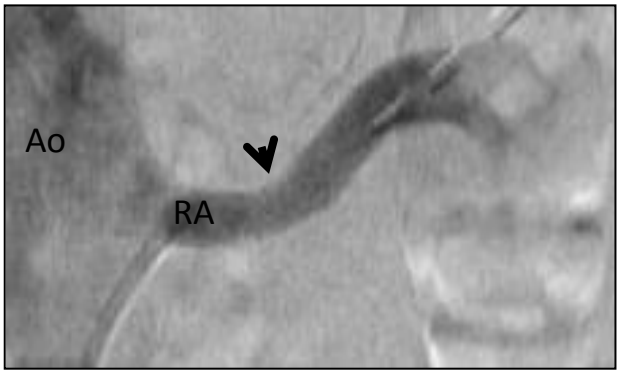


Figure 2. The below frame is from pre-intervention angiography and confirms severe proximal left renal artery filling defect with approximately 75% diameter stenosis and post-stenotic dilatation. Next image is a digital subtraction angiography frame captured after stent placement, demonstrating resolution of stenosis. [Key: Ao = Aorta. RA = renal artery. Arrow = stenosis. Arrowhead = stent location (stent is poorly visualized due to low contrast usage.)]





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