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Renal Artery Stenosis in a Young Female without Fibromuscular Dysplasia with Literature Review

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ABSTRACT: Renal artery stenosis (RAS) is rare in young patients without fibromuscular dysplasia (FMD). RAS is primarily classified as having two major etiologies, namely, atherosclerosis and FMD, with 90% and 10%, respectively. We report a case of a female in her mid 20s who developed hypertension due to RAS with no evidence of FMD or underlying renal dysfunction and underwent successful angioplasty and stenting.

KEYWORDS: renal artery stenosis, fibromuscular dysplasia, atherosclerosis

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Case Report

We present a case of an African-American female in her mid 20s with a history of smoking and uncontrolled hypertension who presented with intermittent abdominal pain for three years. The patient had past medical history significant for hypertension, smoking, and depression and no family history of premature coronary artery disease. The patient additionally had no past medical history significant for various vasculitides, such as Kawasaki's disease, Moyamoya disease, Williams syndrome, or any other pathology, which could have contributed to her clinical presentation. The patient had smoked three cigarettes a day for the past four years and drinks alcohol socially. She was on amlodipine 10 mg oral daily. She was sent from her primary medical doctor's office after a renal ultrasound showed a hemodynamically significant left renal artery stenosis (RAS) in the mid aspect of the renal artery with a left resistive index of 0.3, left renal/aortic ratio of 3.91, and left mid renal artery velocity Sys (systolic)/Dias (diastolic) of 313/213.

The patient's vital signs on admission showed a blood pressure of 166/105, heart rate of 75, respiratory rate of 16, and body temperature of 98.7 °F. The initial electrolyte profile of the patient was as follows: sodium 137, potassium 3.8, chloride 105, bicarbonate 25, blood urea nitrogen (BUN) 9, creatinine 0.68, glucose 89, calcium 8.5, magnesium 1.9, and phosphorous 2.9. The renin assay was 1.4 ng/mL/hour and the plasma aldosterone concentration was 7.1 ng/dL and the left kidney size was 13.4 × 4.2 cm, while the right kidney size was 10.1 × 4.0 cm. The right renal velocity was 80 cm/second. Physical examination was within normal limits, and no

abdominal bruits were appreciated. She had a 2-dimensional echocardiogram (2D Echo), which showed mildly increased left ventricular wall thickness with an ejection fraction of 65%. The electrocardiogram showed normal sinus rhythm with no significant abnormalities. The patient underwent a renal artery catheterization the subsequent day. Based on angiography and subjective analysis, a severe 99% mid left RAS with significant poststenotic dilatation was appreciated. Initially, the interventionist decided to perform a balloon angioplasty. However, the patient was noted to have a gradient more than 24 mmHg post angioplasty and hence a stent was also successfully placed. Following the intervention, there was an excellent angiographic appearance with a 0% residual stenosis (Fig. 2). Following the procedure, the patient was instructed to continue her antihypertensive regimen of amlodipine 10 mg PO daily. After stenting, the patient's blood pressure normalized to 122/82 in the hospital prior to discharge. The patient initially agreed for a follow-up on an outpatient basis with her cardiologist; however, after several months, the patient failed to follow-up with her primary care physician as well as her cardiologist.

This patient illustrates a case of hypertension secondary to RAS not caused by fibromuscular dysplasia (FMD) that is more typical for this age group. This case is unique as it describes the case of a young female who presented with hypertension that was unusual for her age and risk factors, without any evidence of atherosclerotic disease or FMD on angiography, which completely resolved after balloon angioplasty with stent placement.



Discussion

Pathophysiology of RAS. RAS is best defined as the “narrowing of the renal arteries caused by heterogenous group of conditions including atherosclerosis, FMD, vasculitis, neurofibromatosis, congenital bands, and extrinsic compression and radiation”.¹ Atherosclerosis is the most common cause accounting for 90% of the lesions causing obstruction to the arteries. The prevalence of Atherosclerotic Renal Artery Stenosis (ARAS) rises with age as well as with concomitant conventional cardiovascular risk factors. It is associated with hypertension and chronic kidney disease and seen in more than 40% of patients with peripheral vascular disease as well as 10%–14% of patients undergoing cardiac catheterization with renal angiography. In addition, “oxidative stress has been implicated in ischemic and hypertensive parenchymal renal injury related to ARAS”.¹ “Historical data show that up to 27% of patients with ARAS will develop chronic renal failure within 6 years; additionally, studies have revealed that it is a cause of end-stage renal disease in 14% of patients in whom dialysis was newly initiated”.¹

Moreover, the pathophysiology of the renin-dependent hypertension in patients with RAS due to fibromuscular dysplasia was first outlined by Goldblatt in the 1930s. His work has been expanded on to propose three distinct phases of renovascular hypertension that have previously been established in animal models. The stages include stage I (acute occlusion), stage II (occlusion for days/weeks), and stage III (occlusion prolonged for months). Elevated levels of both renin and angiotensin II characterize stages I and II. These elevated levels lead to elimination of obstruction and therefore in turn lead to normalization of both blood pressure and plasma renin/angiotensin II levels.¹ In contrast, in stage III, plasma renin/angiotensin levels are no longer elevated and elimination of the obstruction does not lead to normalization of blood pressure”.¹

Fibromuscular dysplasia. FMD is characterized by abnormal cell growth in the walls of arteries of the body. The majority of patients diagnosed with FMD are females with data from the United States FMD patient registry, suggesting that patients are typically diagnosed in their early 50s.² FMD most commonly affects the renal, carotid, and vertebral arteries, and it is classified according to the layer of artery wall most involved.² The most common is medial fibroplasia. A number of theories have been proposed regarding its cause including environmental factors, such as smoking, estrogen, as well as genetic factors; however, it continues to be an area of investigation.² Signs and symptoms of FMD in the renal vasculature include high blood pressure, abdominal bruits, renal artery aneurysm, and renal artery dissection. Catheter-based angiography is the most accurate imaging technique, and angioplasty is recommended for patients with renal artery FMD who have uncontrollable blood pressure, intolerance to medications, or declining kidney function.²

Atherosclerotic renal artery stenosis. ARAS most commonly contains the ostium and the proximal third of the renal

artery, as well as the adjoining aorta.¹ However, segmental and diffuse intrarenal atherosclerosis may also be appreciated, especially in severe cases. On the basis of the American Heart Association, there are several clinical clues that help diagnose ARAS. These include the following:

1. Onset of hypertension before 30 years old or severe hypertension after 55 years old (Class I, level of evidence [LOE] B);
2. Accelerated, resistant, or malignant hypertension (Class I, LOE C);
3. Development of new azotemia or worsening renal function after administration of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (Class I, LOE B);
4. Unexplained atrophic kidney or size discrepancy >1.5 cm between kidneys (Class I, LOE B);
5. Sudden, unexplained pulmonary edema (Class I, LOE B);
6. Unexplained renal dysfunction, including patients starting renal replacement treatment (Class IIA, LOE B);
7. Multivessel coronary artery disease or peripheral arterial disease (Class IIB, LOE B); and
8. Unexplained congestive heart failure or refractory angina (Class IIB, LOE C).

Although these clinical clues are useful in diagnosing patients with RAS, the Joint National Committee states that “more extensive testing in patients with identifiable causes of ARAS is typically not necessary unless blood pressure control is not achieved while the patient is receiving maximal antihypertensive therapy”.¹

Several methods had been used as screening tools to help with the detection of ARAS, which include, but are not limited to: “magnetic resonance angiography (MRA), helical computed tomographic angiography (CTA), Doppler ultrasonography, renal scintigraphy (captopril scan), invasive angiography, peripheral renin levels, and renal vein renin sampling”.¹ In order for an individual imaging study to be considered optimal, they must meet certain objectives like “characterization on the basis of anatomic and hemodynamic severity of ARAS, anatomic consequences on the artery and on the kidney itself, functional and cellular consequences of ARAS on the kidney and identification of criteria associated with renal impairment related to renovascular disease”.¹ The test of choice will basically depend on the local availability and clinical expertise.

Ultrasonography is the primary imaging study used to detect ARAS. Its benefits are that it is widely available, safe, and inexpensive, but results depend on the operator and have suboptimal accuracy that ranges from 60% to 90%.¹ In RAS, “spectral broadening and increased velocity on ultrasound are markers of hemodynamically significant stenosis. When using duplex Doppler ultrasonography, utilization of the renal resistive index can predict the outcome after revascularization, showing that a higher resistive index is associated with diminished predicted benefit from revascularization”.¹ In a study of



almost 6000 patients with hypertension and clinical features, suggestive of atherosclerotic renovascular disease, 131 patients who had RAS and underwent technically successful angioplasty had poor outcomes with a resistive index of 0.5. Outcomes were better among the 96 patients with a resistive index of less than 0.5.⁴ Thus, this is not a broadly useful parameter for predicting outcome after revascularization.

CTA is another important tool utilized to aid in the diagnosis of RAS; however, CTA is contraindicated in patients with contrast allergy and has the possibility of causing contrast-induced nephropathy in patients with impaired renal function.¹ CTA can detect small accessory renal arteries because of high spatial resolution, and this modality is preferred in many clinical situations (eg, implanted devices, claustrophobia) but has “less specificity than MRA for detecting hemodynamically significant ARAS”.¹

Using arteriography as the gold standard, MRA has a reported sensitivity and specificity of 90% and 100%, respectively. It does not require the use of iodinated contrast or radiation, resulting in lower contrast reactions; however, there are concerns about gadolinium-associated complications including nephrogenic systemic fibrosis, which have greatly reduced its application for renovascular disease, primarily in patients with reduced renal function.¹

Angiography is helpful in evaluating a patient with ARAS, as it assesses the severity and detects intrarenal vascular abnormalities and anatomic abnormalities. It is true that using “digital subtraction angiography improves contrast resolution and may decrease the volume of contrast needed to as little as 15 mL, but because it is invasive there are several risks such as arterial puncture and manipulation of catheter/wire, it can result in arterial trauma, spasm or thromboembolic phenomena; however, it has the advantage that in patients with renal impairment or contrast allergy, carbon dioxide can be used to avoid nephrotoxicity”.¹

Because of the potential for harm from invasive procedures, only those patients who are thought to have high likelihood of benefiting from the procedure are tested. These include patients with failure of optimal medical therapy with secondary causes being evaluated, intolerance to optimal medical therapy, and suspected fibromuscular disease in a young person in an attempt to limit the need for lifelong antihypertensive therapy.

Treatment: medical therapy vs revascularization. Medical therapy and revascularization approach have been used for the management of RAS. These patients necessitate thorough medical therapy. “Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are recommended for controlling hypertension and reducing clinical events in those with known cardiovascular disease.” But its use is with caution, as it may progress to overt renal failure, especially in patients with severe bilateral RAS or advanced chronic kidney disease.⁵

A more controversial area is the use of renal artery revascularization as a therapeutic option in these patients with RAS.

The 2006 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on peripheral artery disease state that testing for RAS is only indicated if a corrective procedure is to be performed once clinically significant renovascular disease is detected. In the medical literature, it is shown that patients with incidentally discovered ARAS do not require therapy directed at the renal vasculature since there is evidence that renal artery revascularization in such patients does not improve blood pressure or other outcomes in this setting.¹

Several small-randomized control trials in the 1990s demonstrated only minor differences in BP attributable to revascularization, although crossover rates from medical therapy arms were substantial, ranging from 24% to 44%.⁵ The Stent Placement for Atherosclerotic Renal Artery Stenosis (STAR) and Angioplasty and Stenting for Renal Atherosclerotic Lesions (ASTRAL) were published in 2009 in the general medical literature. Both of these studies concluded that revascularization for atherosclerotic renovascular disease provides no benefit. Recent studies also indicate that after renal artery stent placement, inflammatory injury markers and GFR do not recover, despite increasing blood flow and reversing tissue hypoxia.³

Antihypertensive drugs can effectively control the blood pressure in many patients with renovascular hypertension, and it is unclear that correction of a stenosis (with either percutaneous or surgical therapy) frequently results in additional long-term benefit. Also, consistent use of statins, balanced glycemic control, and smoking cessation counseling are of great significance. The ongoing randomized, multicenter *Cardiovascular Outcomes in Renal Atherosclerotic Lesions* (CORAL) trial is evaluating whether or not percutaneous revascularization of renovascular disease is superior to optimal therapy in preventing cardiovascular outcomes.¹ The CORAL results show that renal artery stenting does not reduce adverse outcomes in patients that present with ARAS and hypertension or chronic kidney disease, compared with medical therapy alone. Although associated with a modest reduction in systolic blood pressure, stenting does not reduce the risk of cardiovascular or renal events.³

Renal artery stenting procedures have significantly increased as one approach to treat this clinical problem. Developing both noninvasive and invasive predictive tools to better identify which patient will respond to renal revascularization will also be beneficial.⁴

Conclusion

ARAS is not common in young females. RAS is a medical condition with complex pathophysiology that involves early recognition and effective medical therapy to prevent future cardiovascular events. This is still a problem for clinicians with no clear consensus on how to investigate and assess the clinical significance of stenotic lesions and manage the findings. RAS caused by FMD is likely more common than previously appreciated that should be actively looked for in younger



hypertensive patients and can be managed successfully with angioplasty.⁵

Author Contributions

Conceived and designed the experiments: PP, MC. Analyzed the data: PP. Wrote the first draft of the manuscript: PP, MC. Contributed to the writing of the manuscript: PP, MC, DG. Agree with manuscript results and conclusions: PP, MC, DG, JK, FS. Jointly developed the structure and arguments for the paper: MC, PP, JK, DG. Made critical revisions and approved final version: MC, DG. All authors reviewed and approved of the final manuscript.

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