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Pickering Syndrome precipitated by Angiotensin Converting Enzyme Inhibitor

Pramod Theetha Kariyanna[1,*], Apoorva Jayarangaiah[2], Robert Adrah[3], Abhishek Sharma[4], Debabrata Sen[3]

[1]Department of Internal Medicine, State university of New York (SUNY)- Downstate Medical center, Brooklyn, New York, U.S.A.
[2]Department of Internal Medicine, Marshfield Clinic- St. Joseph Hospital, Marshfield, Wisconsin, U.S.A.
[3]Department of Internal Medicine, Brookdale University Hospital and Medical Center, Brooklyn, New York, U.S.A.
[4]Division of Cardiology, Department of Internal Medicine, State university of New York (SUNY)- Downstate Medical center, Brooklyn, New York, U.S.A.
*Corresponding author: drtkpram@gmail.com

Abstract Pickering syndrome is an under recognised cardio-renal syndrome where life threatening flash pulmonary edema develops in the setting of diastolic dysfunction of the heart. Renal artery stenosis induced activation of sympathetic nervous system and renin-angiotensin-aldosterone system result in fluid retention; such fluid retention in the setting of diastolic dysfunction results in flash pulmonary edema. Most patients who present with pickering syndrome have normal coronary circulation and left ventricular systolic function. We here present a case of pickering syndrome that was precipitated by initiation of angiotensin converting enzyme inhibitor therapy in a patient with undiagnosed unilateral renal artery stenosis. The incidence of flash pulmonary edema decreases on revascularization of renal artery stenosis. Underlying renal artery stenosis should be suspected in a patient with recurrent flash pulmonary edema as such patients merit from revascularization of renal artery stenosis. To the best of our knowledge we are the first to report angiotensin converting enzyme inhibitors as a precipitator of pickering syndrome.

Keywords: *pickering syndrome, renal artery stenosis, diastolic dysfunction of heart, angiotensin converting enzyme inhibitors, renal artery revascularization*

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1. Introduction

Pickering syndrome is a less know cardio-renal syndrome where patients with renal artery stenosis (RAS) who have an underlying diastolic dysfunction develop flash pulmonary edema (FPE) upon slightest fluid overload [1]. Owing to their renal and cardio-protective properties angiotensin converting enzyme inhibitors (ACEI) are commonly used medications in patients with chronic renal failure and heart failure [2,3,4]. Bilateral RAS is an absolute contraindication for initiation of ACEI. Due to the blockade of angiotensin II induced efferent arteriolar vasoconstriction a slight fall in glomerular filtration rate (GFR) is expected to happen upon initiation of ACEI therapy [5]. Such a decrease in GFR can result in activation of sympathetic nervous system and renin-angiotensin-aldosterone system resulting in salt and water retention and this may precipitate pickering syndrome.

2. Case Presentation

An 80-year-old-woman with past medical history of hypertension, hyperlipidemia, non-ST segment elevation myocardial infarction (NSTEMI) 24days ago presented with anuria, nausea/vomiting and weight gain for four days. She underwent percutaneous coronary intervention with drug eluting stent implantation 24 days ago and subsequently discharged on aspirin (81 mg once a day, orally), clopidogrel (75 mg once a day, orally), metoprolol (50 mg once daily, orally), atorvastatin (80 mg once daily, orally), furosemide (40 mg once daily, orally) and quinapril (10 mg twice daily, orally). At the time of presentation physical examination revealed a blood pressure of 178/99 mm of Hg, jugular venous distention, grade II edema till knees and rales in bilateral posterior lung fields.

Blood urea nitrogen (BUN) and serum creatinine 24 days prior to presentation were 30 mg/dl and 0.8 mg/dl respectively; the calculated glomerular filtration rate (GFR) was > 60 ml/min/1.73 sq. ms. She presented with frank renal failure with BUN of 91 mg/dl, serum creatinine of 8.6 mg per dl and GFR of 5 ml/min/1.73 sq. ms (Figure 1 and Figure 2) Transthoracic echocardiography obtained 24 days prior revealed left atrial dilation, left ventricular ejection fraction of 55%, grade 1 diastolic dysfunction, mild fibro-calcific changes of the aortic root and mild mitral annular calcification. Chest radiography revealed diffuse bilateral infiltrates (Figure 3), which along physical examination indicated biventricular failure. Furosemide and quinapril were discontinued and patient

was emergently hemodialyzed. Duplex ultrasound revealed right renal artery stenosis (RAS) (Figure 4). Patient was managed for flash pulmonary edema with diuresis. Serum creatinine levels eventually returned to baseline.

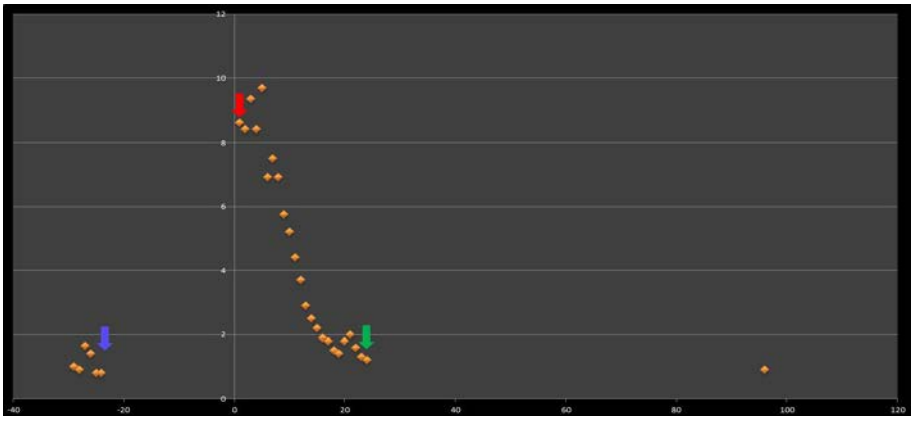

Figure 1. Serum creatinine trend in the patient. Blue arrow indicates serum creatinine levels 24 days prior to presentation (0.8 mg/dl) during which ACEI therapy was initiated. Red arrow indicates serum creatinine (8.6 mg/dl) at presentation and green arrow indicates return of serum creatinine (day 24) after ACEI therapy was discontinued at presentation. X- axis represents days, Y-axis represents serum creatinine level

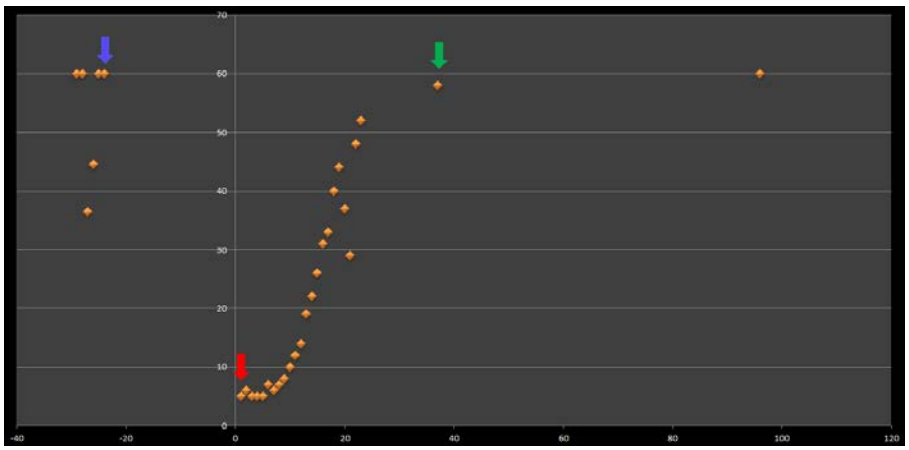

Figure 2. Glomerular filtration rate trends in the patient. Blue arrow indicates a GFR of > 60 ml/min/1.73 sq. ms, 24 days prior to presentation, during which ACEI therapy was initiated. Red arrow indicates a low GFR of of 5 ml/min/1.73 sq. ms at presentation and green arrow represents return of GFR to normal levels upon discontinuation of ACEI in the patient. X- axis represents days, Y-axis represents serum creatinine level

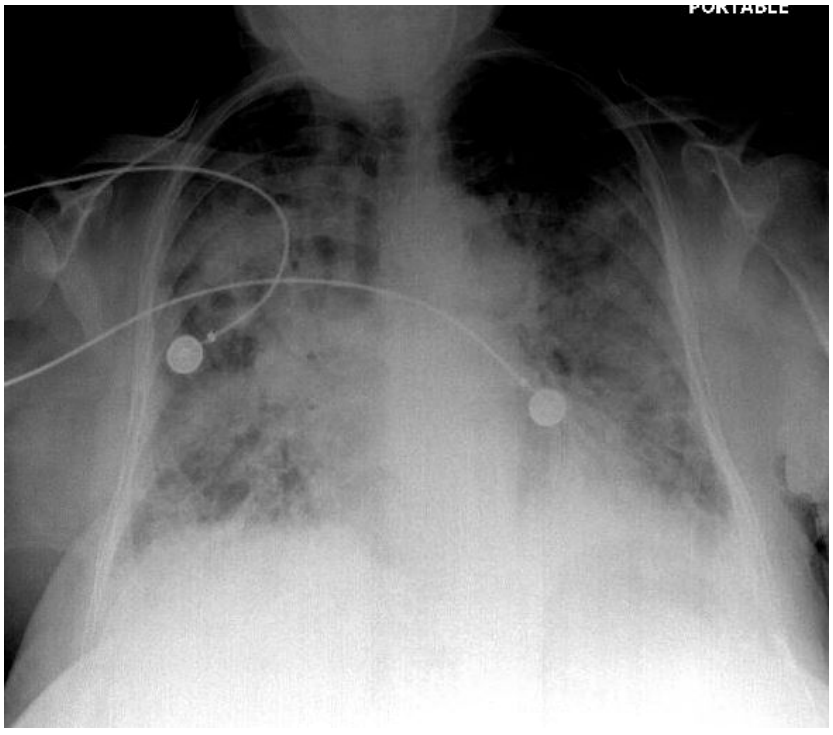

Figure 3. Chest radiography of the patient consistent with bilateral pulmonary edema

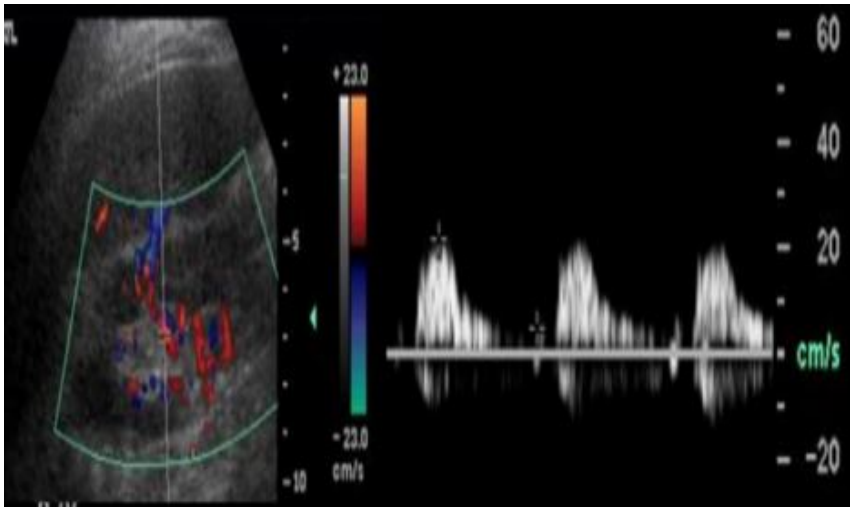

Figure 4. Duplex of right renal artery showing significantly reduced flow (20 cms per second), a finding consistent with renal artery stenosis

3. Discussion

Atherosclerotic renovascular disease accounts for 90% of RAS [6]. RAS is usually asymptomatic but may present with hypertension, renal dysfunction, athero-embolism, proteinuria, and CHF [7]. Hypertension secondary to RAS usually presents in younger individuals with no family history of hypertension, difficult to control hypertension, renal impairment with mild proteinuria and > 1.5 cms difference in kidney function on ultrasonography. Patient with RAS tend to have reversible early deterioration of renal function upon initiation of angiotensin converting enzyme inhibitors (ACEI) [8,9].

In patients who underwent cardiac catheterization for suspected coronary artery disease (CAD), the prevalence of significant RAS (RAS >50%) was found to be 8% [1]. In patient with heart failure, McDowall and colleagues had reported prevalence of RAS to be as high as 34%; however they had excluded patients whose serum creatinine rose previously upon initiation of captopril therapy [10]. Heart failure patients with renal dysfunction have poor clinical outcomes, though it is not clear if the renal dysfunction can be attributed to RAS or if the RAS has contribution in the poor outcomes [11].

Various patho-physiological mechanisms are attributed in development of FPE in patients with bilateral RAS: i) Activation of renin-angiotensin-aldosterone system (RAAS) results in significant sodium and fluid retention [12], ii) decreased renal blood flow and subsequent renal ischemia stimulated sympathetic nervous system and RAAS [13], iii) diastolic dysfunction of heart that ensues as a result of hypertension [14], iv) pulmonary capillary stress failure and increased pulmonary capillary permeability [15], v) absence of pressure natriuresis [16]. The relative lower prevalence of FPE in patients with unilateral RAS as compared to patients with bilateral RAS may partially be attributed to pressure natriuresis is the functionally normal kidney [1].

Fluid overload and diastolic dysfunction appears to play an important role in development of FPE. Two-thirds of a patient's FPE have normal ventricular function [12]. Persistent hypertension results in left ventricular hypertrophy and diastolic dysfunction. Sympathetic activation increases arterial stiffening, and for such an increase in the after load the left ventricle normally compensated by increasing the left ventricular end diastolic volume. This compensation is curtailed by stiff left ventricle in diastolic dysfunction [18,19,20,21]. Sympathetic activation induced tachycardia decreases diastolic left ventricular filling [22]. Underlying ischemic heart disease and decrease diastolic duration impairs normal cardiac perfusion [23]. Left ventricular systolic dysfunction, elevated left ventricular end diastolic pressure and excessive sympathetic activation results in FPE [1,22]. Endothelial dysfunction secondary to elevated neurohumoral mediators such as angiotensin II, endothelin-1 and catecholamines with decreased synthesis of nitric oxide in endothelium is contributory; FPE ensues at intracapillary pressure of 20-25 mm Hg [24]. Following development of FPE, left ventricular function worsens resulting in significant fall in renal perfusion which further triggers activation of the vicious cycle.

Most patients with pickering syndrome present with unprovoked dyspnea secondary to FPE, Pickering et al reported FPE prevalence of 2.3 times prior to presentation [25]. Messerli et al in their case series reported that 93% of patients had recurrent FPE and the remaining 7% a single event prior to diagnosis. Normal left ventricular function and absence of flow limiting coronary artery lesions in the patient population may result in a “false sense of security” for absence of cardiac pathology [1].

Though renal angiogram is the gold standard for diagnosis of RAS, renal duplex scan is an alternate as it is rapid and non-invasive [26]. FPE in patients should be managed as an hypertensive emergency, diuresis to induce sodium and water loss. Antihypertensive medications including ACEI are useful in relieving FPE but they may decrease renal perfusion hence may worsen pulmonary edema [1]. The American College of Cardiology/ American Heart Association recommend percutaneous revascularization in patients who have hemodynamically significant RAS and recurrent, unexplained CHF or pulmonary edema [27]. Failure of pressure natriuresis is contributory in development of pickering syndrome. Hence renal revascularization is beneficial [28,29]. Renal artery stenting is superior to balloon angioplasty for RAS revascularization [27,30,31].

The case of pickering syndrome we present here was precipitated by ACEI in a patient with asymptomatic unilateral RAS and mild diastolic and systolic heart failure.

4. Conclusion

Pickering syndrome, a cardio-renal syndrome is increasingly being reported. Physicians should be mindful of precipitating FPE in patients with asymptomatic RAS in setting of diastolic dysfunction. Disease free coronaries and normal ejection fraction should not mislead the management; the possibility of underlying RAS should be investigated. ACEI may precipitate pickering syndrome in patients with undiagnosed RAS. A renal duplex can help establishing diagnosis of RAS in such patients, who can benefit from renal artery revascularization. To the best of our knowledge we are the first to report angiotensin converting enzymes as a precipitator of pickering syndrome.

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