Transient Renal Artery Stenosis in Pheochromocytoma

FEOKROMOSİTOMADA GEÇİCİ RENAL ARTER STENOZU

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Abstract

Otuz bir yaşındaki erkek hasta hipertansiyon, hipokalemi ve adrenal kitle nedeniyle irdelendi. Klinik bulguların ışığı altında ilk aşamada aldosteronoma düşünülen hastada, diagnostik tetkikler neticesinde feokromositoma ve renovasküler hipertansiyon birlikteliği bulundu. Yüksek katekolamin düzeyleri renal arter vazospasmına ve dolayısı ile renal arter stenozuna neden oluyordu. Oral fenoksibenzamin tedavisi renal arter vazospasmını düzeltti ve yüksek kan basıncını kontrol altına aldı. Feokromositoma ve renal arter stenozu birlikteliği olan hastalarda adrenal kitlenin eksizyonu ile her iki patolojinin aynı anda tedavisi gerçekleşebilir. Böyle durumlarda renal arter lezyonuna yönelik angioplasti veya bypass cerrahisi alfa-reseptör bloker tedavisi uygulanmadan yapılmamalıdır.

Anahtar Kelimeler: Feokromositoma; renovasküler hipertansiyon; renal arter obstruksiyonu

Özet

A 31-year-old man was evaluated for hypertension, hypokalemia and an adrenal mass. Although there was an initial suspicion of an aldosteronoma, diagnostic studies revealed that the patient had coexistence of pheochromocytoma and renovascular hypertension. Renal artery stenosis was due to increased catecholamine release, resulting in renal artery vasospasm. Phenoxybenzamine treatment caused resolution of renal artery vasospasm and controlled hypertension. A corrective procedure such as angioplasty or by-pass grafting should not be performed before a trial of alpha-receptor blocker treatment in coexistent pheochromocytoma and renal artery stenosis patients. Resection of pheochromocytoma results in permanent cure of both conditions.

Key Words: Pheochromocytoma; hypertension, renovascular; renal artery obstruction

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Pheochromocytoma and renal artery stenosis are correctable causes of secondary hypertension. Rarely, these two conditions may coexist together. The clinical presentation of this rare coexistence is complex and accurate preoperative diagnosis is not always possible. The coexistence of pheochromocytoma and renal artery stenosis was reported in 3.7% of pheochromocytoma patients and was accurately diagnosed only in 55% of the reported cases before surgery.[1-4] In case of a preoperative misdiagnosis; postoperative hypertension cure would not be achieved. Uncontrolled catecholamine release during an intervention for renal artery stenosis may cause complications in an unprepared pheochromocytoma patient.[5] The clinical management of an unusual pheochromocytoma patient with hypertension, hypokalemia and elevated plasma renin activity (PRA) is discussed in this report.

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Case Report

A 31-year-old Turkish man was referred for evaluation of hyponatremia and hypokalemia. An elevated blood pressure (BP) was noticed eight months ago. His electrolytes (Na: 135 mEq/L, K: 4.5 mEq/L), complete blood count, BUN, creatinine, calcium level and liver function tests had been normal at that time. He had been prescribed amlodipine 10 mg po qd, and metoprolol

100 mg po qd. He recalled no hypertensive crises. Seven months later, he presented to the emergency room of the referring hospital complaining of fatigue, dry mouth, headache, excessive urination and paresthesias in the extremities. His height was 177 cm, weight: 52 kg, BMI: 16 kg/m^2. His supine BP was 215/140 mmHg, pulse: 108 bpm; his erect BP: 170/120 mmHg and pulse: 108 bpm. Fundoscopic examination showed grade II hypertensive changes. On cardiac auscultation S1 was normal, S2 was loud. The rest of the physical examination was unremarkable. Electrocardiogram showed normal sinus rhythm and findings of left ventricular hypertrophy. Blood chemistries obtained at the referring hospital showed that serum Na: 125 mEq/L (reference range: 135-148 mEq/L, reference values are indicated in parentheses in the following text), K: 2.3 mEq/L (3.5-5.5), BUN: 16 mg/dl and creatinine: 0.9 mg/dl, both were within normal limits. Urine analysis showed (2+) proteinuria. 24 hour urine protein excretion was 2.5 g/day. Spot urine Na level was 64 mEq/L, spot urine K level was 30 mEq/L. With fluid and electrolyte replacement, serum Na level was increased to 134 mEq/L, serum K level to 3.8 mEq/L. Amlodipine 10 mg tablet po qd, and oral K supplements were prescribed. Metoprolol was discontinued. Serum aldosterone level was 47 ng/dl (2-24). An abdominal computerized tomography (CT) showed a 28 mm hypointense (43 Hounsfield Units) adrenal mass.

The patient was referred to our service for evaluation for Conn's Syndrome. Further laboratory tests were obtained. PRA was 9 ng/ml/hr (0.2-3.4). Aldosterone to PRA ratio was 5.2 (reference range: less than 30). High plasma renin activity ruled out Conn's Syndrome. A renin secreting tumor originating from upper part of the left kidney or renal artery stenosis with a coexistent adrenal tumor, either an aldosteronoma or a pheochromocytoma could have caused elevated PRA and aldosterone levels, in the presence of an adrenal mass. Polyuria and paresthesias were likely due to hypokalemia. Renin secreting tumors are localized in the kidney. A renin secreting tumor was not considered further, as our patient had an adrenal tumor. Renal Doppler study showed abnormalities in the lower and middle part of the left renal artery, but not in the superior branch. There was a decrease in the acceleration index (less than 2 m/sec^2; reference value is more than 3 m/sec^2) of the interlober and segmental branches of the left middle and lower renal artery.

The size of both kidneys was within normal limits. Renal Doppler study suggested that renal artery stenosis and elevated plasma renin activity caused secondary hyperaldosteronism and contributed to hypertension. The following tests were obtained to explain the etiology of the adrenal mass. Morning serum cortisol level was 22 µg/dl (5-25). 24 hour urinary aldosterone level was 63 µg/24 hour (reference range: 6-25 µg/day on a normal diet). 24 hour urine for VMA was 26 mg/g/creatinine (1.5-7), metanephrines: 1.7 mg/day (< 1), adrenaline: 28 µg/day (3-18), noradrenaline: 1168 µg/day (15-80), normetanephrines: 7099 µg/day (44-88), suggesting that the left adrenal tumor was a pheochromocytoma. Angiographic study of the renal arteries was not performed because such an investigation carries the risk of adrenal crisis in an unprepared pheochromocytoma patient.[5] Instead, phenoxybenzamine 10 mg po bid was started. When blood pressure and serum K level were normalized, potassium replacement and amlodipine tablet were discontinued. At the phenoxybenzamine 10 mg po tid dose, supine BP was 115/70 mmHg, pulse 80 bpm, serum Na: 140 mEq/L, K: 3.8 mEq/L and Cl: 101 mEq/L. The proteinuria was diminished to 224 mg/day. PRA was 10.3 ng/ml/hr; serum aldosterone level was 25 ng/dl. As plasma renin activity was still elevated, a multislice CT angiography of the left renal artery was performed. The left renal artery and its branches appeared in normal size, shape and caliber (Figure 1) At the phenoxybenzamine 40 mg/day dose, propranolol 20 mg tablet twice daily was initiated, and then the left adrenal tumor was resected. Histopathologic examination confirmed pheochromocytoma. Postoperative serum electrolytes were normal. PRA was 2.52 ng/ml/hr; serum aldosterone level was 3.3 ng/dl (both within normal range). Four years after the

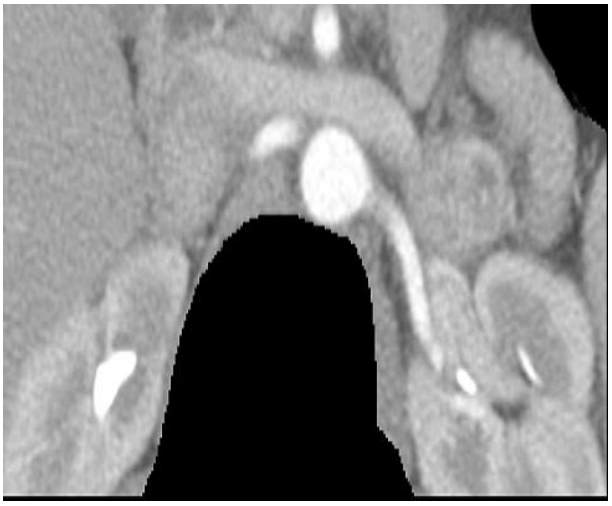

Figure 1. A multislice CT angiogram of the left renal artery. Left renal artery and its branches appear normal. A left adrenal tumor is observed.

surgery, the patient remains normotensive with normal electrolytes and without proteinuria.

Discussion

The presence of hypertension, hypokalemia and an adrenal mass suggests an aldosterone producing adrenal adenoma. Measurement of plasma renin activity is essential in this clinical picture. If PRA is high, aldosteronoma is ruled out and a renin secreting tumor or coexistence of pheochromocytoma and renal artery stenosis should be considered. Only five cases of coexistent pheochromocytoma and primary hyperaldosteronism, either in the form of aldosteronoma or idiopathic hyperaldosteronism have been reported.[6,7] Coexistent renal artery stenosis and aldosteronoma cases also presents with hypertension, hypokalemia and an adrenal tumor. After dilatation of the stenosed artery, plasma aldosterone to renin ratio became elevated in the reported patient who had initially normal aldosterone to renin ratio.[8] The presence of hypokalemia in a pheochromocytoma patient, who is not on diuretics or has no gastrointestinal potassium loss, is a marker for an abnormality in renin-angiotensin-aldosterone axis. Hypokalemia may also be caused by secretion of vasoactive intestinal polypeptide (VIP) from a pheochromocytoma. Smith and coworkers reported a 78 year-old woman with gradual onset of hypokalemia, watery diarrhea and weight loss. Diagnostic studies showed that she had a VIP-producing pheochromocytoma, confirmed histopathologically after surgery.[9] Gill and coworkers suggested that the presence of any of the following findings in a pheochromocytoma patient should initiate a search for renal artery stenosis: elevated serum creatinine level, increased plasma renin activity, radiological findings suggestive of renal artery stenosis, a small kidney, aortorenal atherosclerosis, renal arterial calcification, an extra-adrenal pheochromocytoma at the renal hilum and a large inferior polar adrenal mass compressing renal artery.[1] In view of the clinical presentation of our patient, hypokalemia should be added to this list.

There are several mechanisms that could cause elevated renin secretion and renal artery stenosis in pheochromocytoma patients. Zacherieva and coworkers measured PRA in patients with various types of adrenal tumors. Patients with pheochromocytoma had the highest active renin levels compared with patients who have other types of adrenal tumors, such as cortisol-secreting adrenal adenoma, aldosteronoma and adrenal carcinoma.[10] Catecholamines are physiologic stimulators of renin secretion.[5] Intravenous infusion of epinephrine to dogs is shown to cause renin release and constriction in the main renal artery.[11] Local seepage of vasoactive amines from an adjacent pheochromocytoma into the renal artery or its branches may cause catecholamine-induced vasospasm.[1] Catecholamine induced vasoconstriction could induce a sustained arterial spasm and in the long term may result in a vessel morphology with dysplastic changes in the muscular section of the arterial wall, a progress from spastic phase to organic phase of fibromuscular dysplasia.[1,3] The angiographic appearance of narrowed zone of the renal artery after the administration of epinephrine and the renal artery segment in patients with fibromuscular dysplasia show morphological similarities. Therefore, it was thought that fibromuscular dysplasia may represent a type of hypersensitivity to the effect of epinephrine or other humoral

agents in patients with pheochromocytoma.[3] Stimulation of renal beta adrenergic receptors by catecholamines can increase renin secretion and subsequently that of angiotensin II, which in turn enhances the release of noradrenaline at presynaptic sites. Berard and coworkers studied a pediatric patient with angiographically documented renal artery stenosis and elevated plasma and urinary catecholamines.[12] The patient did not have pheochromocytoma, as no evidence of extraadrenal or adrenal tumor was found after a diligent radiologic search. Excess catecholamine state was attributed to stimulation of catecholamine release by angiotensin II, either through peripherally or centrally. So, catecholamines can stimulate renin angiotensin system and vice versa, elevated angiotensin II levels can stimulate catecholamine secretion. The following are potential mechanisms that can increase plasma renin levels in patients with pheochromocytoma:[1-5]

1) Compression of renal artery by pheochromocytoma.

2) Direct stimulation of renin secretion by elevated circulating catecholamines.

3) Excess circulating catecholamines induce renal arterial vasospasm, reduce blood flow to the kidney and result in renal ischemia.

4) Hyperreninemia as a consequence of decreased plasma volume associated with pheochromocytoma.

5) Hyperreninemia as a response to salt restriction and diuretic treatment recommended for treatment of hypertension in pheochromocytoma.

Coexistence of pheochromocytoma and renal artery stenosis is a rare occurrence. Including our patient, only 93 cases are reported up to date.[1-4,13-17] Of these 93 cases 54% (50 patients) had adrenal pheochromocytoma; 46% (43 patients) had extraadrenal pheochromocytoma. 10 cases (11%) had bilateral pheochromocytoma. Approximately 14% of coexistent pheochromocytoma and renal artery stenosis cases occurred in children.[2,17] Perioperative mortality occurred in two patients in whom pheochromocytoma was not diagnosed preoperatively and they were operated for renal artery stenosis.[3] In contrast, the inability to preoperatively diagnose renal artery stenosis in pheochromocytoma patients is not known to cause any mortality. There was no perioperative mortality in 4 patients in whom the diagnosis of coexisting renal artery stenosis was missed before pheochromocytoma resection.[1] Hypertension will persist postoperatively, if either etiology is not corrected. Extrinsic compression of renal artery is the most common cause of renal artery stenosis in pheochromocytoma patients, observed in 39% of reported cases.[1-4,13-17] Fibromuscular dysplasia of the renal artery has been reported in pheochromocytoma patients.[3] This association is most common in patients with neurofibromatosis, although it has been known to occur with a variety of other familial syndromes.[2,3] Atherosclerotic disease of the renal artery may occur independently from pheochromocytoma in older patients and can cause renal artery stenosis. Renal artery aneurysm, thrombosis of the renal artery, membranous narrowing, intrarenal renal artery atherosclerosis, retroperitoneal fibrous adhesions emanating from pheochromocytoma and post-angiography renal artery dissection-occlusion have been reported as causes of renal artery stenosis in pheochromocytoma patients.[1-5] A patient with von Hippel- Lindau disease and norepinephrine-producing pheochromocytoma had elevated levels of plasma renin activity and aldosterone levels manifested with hypertension and hypokalemia. Angiography did not show renal artery stenosis.[18]

The finding of elevated plasma renin activity is not always diagnostic of renal artery stenosis in pheochromocytoma patients. An imaging modality is necessary to document the presence of renal artery stenosis. In the past, captopril radionuclide scanning used to be the screening test of choice for renal artery stenosis. Renal vein renin ratios and split renal function tests were commonly used to lateralize the renal ischemia and establish the functional significance of the angiographically demonstrated stenosis. Currently, Doppler study of the renal vasculature and magnetic resonance angiography (MRA) are the screening tests of choice. Compared with angiography, Duplex ultrasound

has a sensitivity of 84 to 89% and a specifity of 62 to 99%.[19,20] CT angiography has a sensitivity of 59 to 96% and a specifity of 82 to 99% when compared with conventional angiography.[20] MRA has a sensitivity of 90 to 100% and a specifity of 76 to 94% for detection of renal artery stenosis.[20] MRA or CT angiography has additional benefits over Doppler ultrasonography and renal scintigraphy in the diagnosis of renovascular hypertension. In a series of 77 hypertensive patients who did not respond to three-drug antihypertensive therapy, MRA showed that 44% had renal artery disease and 9% had an adrenal mass. Further evaluation revealed that 57% of identified adrenal masses were responsible for hypertension and would have been missed if either renal scintigraphy or Doppler ultrasound studies were employed as a screening modality.[21] CT angiography requires a bolus of contrast agent, making it a less attractive option in patients with renal insufficiency or who are at risk for renal insufficiency. With the advent of multidetector CT scanners, less amount of contrast is administered and higher quality images are obtained in shorter period of time. Renal Doppler study suggested involvement of the left middle and lower segmental branches of the left renal artery in this case. Local renal arterial vasoconstriction due to elevated catecholamine levels was probably the cause of elevated renin levels in our patient. In patients with renal artery stenosis, conventional angiography is currently recommended only if a revascularization procedure is planned.[20] MRA or Duplex ultrasound supplanted conventional angiography in making the diagnosis of renal artery stenosis. Invasive procedures, including arterial angiography may aggravate a hypertensive attack in an unprepared patient with pheochromocytoma;[5] therefore it was not performed in this case. Alpha receptor blocker treatment was instituted and resulted in normalization of blood pressure and serum potassium levels. Then a multislice CT angiography was obtained and showed resolution of renal artery stenosis, though plasma renin activity was still elevated. Phenoxybenzamine treatment with its α-adrenergic receptor blocking properties may have prevented renal artery vasoconstriction. Acting through β-adrenergic receptors elevated catecholamine levels may have directly stimulated the secretion of renin levels from juxtaglomerular apparatus in this patient.[5]

In a pheochromocytoma patient with radiographically documented renal artery stenosis, spontaneous hemorrhagic necrosis of the pheochromocytoma occurred. As a consequence, excess catecholamine secretion diminished, elevated renin levels decreased and resolution of renal artery stenosis was observed in angiography.[13] As observed in this convincing example from the literature and in our case, vasoconstriction of the renal artery and resulting hyperreninemia may be temporary.[1-4,13] The resolution of renal artery stenosis was observed in our case with the administration of phenoxybenzamine, although renin levels remained elevated. Physicians must be aware of this response, otherwise they may recommend an unnecessary renal vascular intervention. Renal artery by-pass grafting, balloon angioplasty or stent placement should not be instituted before a trial of α-adrenergic blockers in pheochromocytoma patients who have coexistent renal artery stenosis. As observed in our case, resection of pheochromocytoma leads to permanent cure of renal artery stenosis and results in normalization of elevated plasma renin levels.

REFERENCES

1. Gill IS, Meraney AM, Bravo EL, Novick AC. Pheochromocytoma coexisting with renal artery lesions. J Urol 2000; 164:296-301.
2. Camberos A, Bautista N, Rubenzik M, Applebaum H. Renal artery stenosis and pheochromocytoma: coexistence and treatment. J Pediatric Surg 2000; 35:714-6.
3. Kaufmann JJ. Pheochromocytoma and stenosis of the renal artey. Surg Gynecol Obstet 1983;156:11-5.
4. Jensen SR, Novelline RA, Brewster DC, Bonventre JV. Transient renal artery stenosis produced by a pheochromocytoma. Radiology 1982;144:767-8.
5. Young JB, Landsberg L. Catecholamines and the adrenal medulla. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, editors. Williams Textbook of Endocrinology. 9th ed. Philadelphia: W.B. Saunders Co; 1998. p.707-28.
6. Tan GH, Carney JA, Grant CS, Young WF Jr. Coexistence of bilateral adrenal phaeochromocytoma and idiopathic hyperaldosteronism. Clin Endocrinol (Oxf) 1996:44:603-9.
7. Gordon RD, Bachmann AW, Klemm SA, et al. An association of primary aldosteronism and adrenaline-secreting phaeochromocytoma. Clin Exp Pharmocol Physiol 1994; 21:219-22.

8. Glodny B, Cromme S, Wortler K, Herwig R, Kisters K, Winde G. Conn's syndrome and bilateral renal artery stenosis in the presence of multiple renal arteries. J Endocrinol Invest 2001;24:268-73.
9. Smith SL, Slappy AL, Fox TP, Scolapio JS. Pheochromocytoma producing vasoactive intestinal peptide. Mayo Clin Proc 2002;77:97-100.
10. Zacharieva S, Atanassova I, Orbetzova M, et al. Circulating vascular endothelial growth factor and active renin concentrations and prostaglandin E2 urinary excretion in patients with adrenal tumors. Eur J Endocrinol 2004;150:345-9.
11. Abrams HL, Boijsen E, Borgström KE. Effect of epinephrine on the renal circulation. Radiology 1962;79:911-22.
12. Berard E, Candito M, Diaine B, et al. Increased urinary catecholamines in a hypertensive child with renal artery stenosis. Pediatr Nephrol 1996;10:761-3.
13. Kishikawa H, Tsuji H, Takagi I, et al. Hemorrhagic necrosis of pheochromocytoma associated with reversible renal artery stenosis. Jpn J Surg 1986;16:46-51.
14. Del Giudice A, Bisceglia M, D'Errico M, et al. Extra-adrenal functional paraganglioma (phaeochromocytoma) associated with renal-artery stenosis in a pregnant woman. Nephrol Dial Transplant 1998;13:2920-3.
15. Blasi C, D'Amore F, Delle Fave G, et al. A case of pheochromocytoma with renal artery stenosis and post-surgical watery diarrhea. Horm Res 2001;56:130-3.
16. Kuzmanovska D, Sahpazova E, Kocova M, Damjanovski G, Popov Z. Phaeochromocytoma associated with reversible renal artery stenosis. Nephrol Dial Transplant 2001;16:2092-4.
17. Chotsampancharoen T, Patrapinyokul S, Reegkling C, Vachvanichsanong P. Impaired differential renal function in a child with pheochromocytoma. J Hum Hypertens 2005;19:751-4.
18. Lenz T, Thiede HM, Nussberger J, Atlas SA, Distler A, Schulte KL. Hyperreninemia and secondary hyperaldosteronism in a patient with pheochromocytoma and von Hippel-Lindau disease. Nephron 1992;62:345-50.
19. Cantwell-Gab K. Renal artery evaluation. In: Strandness DE editor. Duplex scanning in vascular disorders. 3rd ed. Philadelphia: Lippincott Williams&Wilkins Co; 2002. p.301-18.
20. Olin JW. Renal artery disease: diagnosis and management. Mt Sinai J Med 2004;71:73-85.
21. Tello R, Chaoui A, Hymphrey M, et al. Incidence of adrenal masses in patients referred for renal artery stenosis screening mr. Invest Radiol 2005;36:518-20.