Case Reports

Pheochromocytoma with Renal Artery Stenosis and High Plasma Renin Activity

Miyuki ISHIBASHI, M.D., Akiteru TAKEUCHI, M.D., Shinji YOKOYAMA, M.D.,
Tohru YAMAJI, M.D., Tsuneto TSUCHIMOGI, M.D., Toshiyuki
TANAKA, M.D., Hiroshi KURIHARA, M.D.,
*and Masao IKEDA, M.D.**

SUMMARY

An unusual case of pheochromocytoma is described in this communication. Besides a chain of typical clinical pictures and laboratory findings which suggested a catecholamine-producing tumor, the left renal artery stenosis was demonstrated by an aortography and the plasma renin activity was consistently elevated. Surgery revealed the left renal artery was embedded in the tumor mass, originated from the left adrenal gland, resulting in a high degree of constriction of the vessel. Following the removal of the tumor, blood pressure immediately returned to normal, however, plasma renin activity remained elevated as long as 9 months of the follow-up study. The second aortography performed 14 months after the operation failed to demonstrate the left renal artery stenosis and subsequent studies revealed that plasma renin activity was gradually declining to upper normal levels. It is suggested that an excess of catecholamines secreted by the tumor was responsible for hypertension in this case, and that another factor, probably renal artery stenosis, was involved in the elevation of plasma renin activity, although this high renin activity was maintained for more than 9 months following the tumor extirpation.

Additional Indexing Words:

Serum catecholamine concentration Epinephrine Norepinephrine
Aldosterone Benign pheochromocytoma Phenoxybenzamine
Propranolol Angiography Vena caval catheterization

PHEOCHROMOCYTOMA may be associated with renal artery alterations. We have recently experienced a patient, whose renal artery was com-

From the Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan.

* Associate Professor of Medicine.

This case was preliminarily reported at the 67th Kanto-Ko-Shin-Etsu Regional Meeting of Japanese Circulation Society on February 24, 1973.

Received for publication December 7, 1974.

pressed by an intra-adrenal pheochromocytoma. Her high blood pressure was corrected to the normal level by the excision of the tumor, however, she showed high plasma renin activity before the surgery and during the 9 months follow-up after the tumor removal. The present paper describes this unusual case.

CASE REPORT

A 16-year-old girl was admitted to the Tokyo University Hospital on August 8, 1972, complaining of repeated attacks of syncope, headache, palpitation and excessive sweating of 5 years' duration. She visited a physician in January, 1971, and hypertension, 180 mmHg systolic, was first noticed. She was treated with a daily dose of 0.4 mg reserpine without a remarkable success. On June 20, 1972, she was admitted to the Tokyo Second National Hospital because of a deterioration in her symptoms. Her blood pressure was 216/114 mmHg in supine position with the pulse rate of 140/min. Urinalysis revealed a proteinuria, with normal PSP excretion and creatinine clearance. Intravenous phentolamine injection (5 mg) resulted in a transitory fall in blood pressure from 206/155 to 132/78. A 24-hour urinary excretion of norepinephrine and epinephrine was elevated, suggesting a diagnosis of pheochromocytoma. In an attempt to visualize a tumor, a retroperitoneal pneumography was performed, however, the tumor shadow was not demonstrated. A renogram and an intravenous pyelogram also failed to show the tumor contour. The left kidney was smaller in size than the right on renal scan, although the difference was not significant. During the period of her admission, the patient had a right retinal hemorrhage and the treatment with 20 mg/day phenoxybenzamine was started. This regimen elicited a definite effect on her blood pressure. She was transferred to our hospital for further examination.

On admission, the patient was a thin girl, 163 cm in height and 41 Kg in weight. Her skin was pale and moist with no pitting edema. Physical examination revealed a labile hypertension; the blood pressure was 168/112 mmHg in supine position and precipitously dropped to 62/54 mmHg on standing. Furthermore, her blood pressure was found to fluctuate by 40–50 mmHg within a few minutes. The pulse rate was 120/min. Fundoscopy showed cotton-wool patches and hemorrhage in the posterior retinal pole of her right eye. Lung and heart were normal, and no tumor was palpable in abdomen. No vascular bruit was audible over the renal area. Neurological examination was negative.

Laboratory findings were as follows; hemoglobin 13.9 Gm/100 ml; red blood cell 4,460,000; hematocrit 41.0%; reticulocyte 11%; white blood cell 8,200, with a normal hemogram. Erythrocyte sedimentation rate was 78 mm/hr and C-reactive protein was negative. Serum total protein was 8.68 Gm, cholesterol 260 mg, blood urea nitrogen 11.8 mg, and creatinine 0.7 mg per 100 ml. Serum sodium was 144 mEq, potassium 5.1 mEq and chloride 102 mEq per liter. Serum calcium was 10.2 mg, and phosphorus 4.8 mg per 100 ml with normal % tubular reabsorption of phosphorus. An oral glucose tolerance test (100 Gm) was normal. Urinalysis showed a moderate proteinuria; no abnormality was present in the sediment. The chest roentgenogram was normal. The electrocardiogram revealed a sinus tachycardia.

Table I. A 24-Hour Urinary Excretion of Catecholamines Studied on 3 Successive Days

Preoperation		Postoperation	
Norepinephrine	Epinephrine	Norepinephrine	Epinephrine
3,195 $\mu\text{g/day}$	393 $\mu\text{g/day}$	8.2 $\mu\text{g/day}$	0.9 $\mu\text{g/day}$
863	68	5.5	1.1
3,287	153	4.8	0.9
(<100)	(<10)	(<100)	(<10)

Normal ranges are given in parentheses.

Table II. Peripheral Plasma Renin Activity and Serum Aldosterone Levels in Recumbent Position

Date	Renin Activity	Aldosterone Concentration
Preoperation		
Aug. 21, 1972	2.5 ng/ml/hr	28.4 ng/100 ml
Aug. 22, 1972	3.2*	
Postoperation		
Nov. 15, 1972	6.0	
Jul. 24, 1973	2.2	
Jul. 16, 1974	1.8	2.0
Normal Range	0.5-1.5	<15

* It dropped to 1.1 ng/ml/hr, 30 min after 5 mg propranolol injection and to 1.7 ng/ml/hr, 60 min after 10 mg propranolol injection.

Circulating levels of catecholamines were high; norepinephrine was 18.4 $\mu\text{g/L}$, and epinephrine 0.8 $\mu\text{g/L}$. A 24-hour urinary excretion of catecholamines on 3 determinations was elevated (Table I). On 8-10 Gm/day sodium intake and with 20 mg/day phenoxybenzamine administration, elevation of both plasma renin activity and serum aldosterone levels was noted. Plasma renin activity fell down in response to the injections of 5 or 10 mg propranolol, a beta-adrenergic blocking agent (Table II). Total blood volume determined by dye dilution was 1.99 L, equivalent to 48.5 ml/Kg of body weight. Plasma cortisol levels as well as urinary excretion of 17-OHCS and 17-KS were normal.

Abdominal aortography revealed that the left renal artery was tapered in its distal portion and the excretory phase of the left kidney was slightly delayed (Fig. 1). The left kidney was 11.5 cm in length and 5 cm in width by measurement, and the right kidney was 12 cm, and 6 cm, respectively. No evidence of a suprarenal mass was obtained.

Vena caval catheterization was performed for determining circulating catecholamines in plasma samples taken at the different levels of the caval and renal veins. As shown in Fig. 2, serum norepinephrine concentrations were elevated in all samples and a definite high value was obtained in the sample from the left renal vein.

Operation was carried out on October 12, 1972. An oval intra-adrenal tumor,

Fig. 1. Preoperative abdominal aortogram: Note a marked distal stenosis of left renal artery.

Fig. 2. Norepinephrine concentrations ($\mu\text{g/L}$) in plasma samples collected by the caval catheterization. Some samples were taken in duplicate and the sample from the right renal vein was not obtained because of complaints of the patient.

4 cm in diameter and 45 Gm in weight, was found in the hilar region of the left kidney, arising from the inferior portion of the left adrenal gland with inferior extension to the left renal artery. The left renal artery was completely embedded in the capsule of the mass. The tumor was carefully dissected from the renal artery, aorta and then, the veins draining into the left renal vein and was removed together with the left adrenal gland. The diameter of the left renal artery was reduced to approximately 3 mm. Immediately after the excision of the tumor, the blood pressure fell down dramatically and became stable around 100 mmHg systolic, and neither nephrectomy nor patch angioplasty was tried. Histological examination of the tumor disclosed the typical picture of a benign pheochromocytoma and microscopic examination of the biopsy specimen from the left kidney revealed no evidence of ischemic change.

The patient's postoperative course was uncomplicated, with the blood pressure in the vicinity of 110/70 mmHg. The 24-hour urinary excretion of catecholamines as well as total blood volume returned to normal (Table I). Serum electrolytes concentrations and urinary excretion of 17-OHCS were normal. Plasma renin activity, however, remained elevated as long as 9 months after the excision of the tumor (Table II), while her blood pressure was normal.

An abdominal aortography was performed again in December, 1973, 14 months after the tumor removal. Her left renal artery appeared normal and no stenosis was visualized. Plasma renin activity, on the other hand, fell to 1.8 ng/ml/hr in July, 1974 (Table II).

DISCUSSION

Pheochromocytoma and renal artery stenosis are unusual association. To date only 15 cases of such a combination have been documented since the first report of Rosenheim *et al.*¹⁾⁻¹²⁾ The common mechanism involved is a direct compression of renal artery by the tumor mass,^{1),3)-8),11),12)} and, in some cases, stenosis could be ascribed to chronic exposure of renal artery to high levels of circulating catecholamines.^{2),9)} In our case described above, a constricture of the left renal artery was occasioned by a compression by the tumor mass surrounding the vessel. The tumor was originated from the left adrenal with inferior extension to renal artery. A similar case was reported by Weber *et al.*⁴⁾

It was hard to determine whether renal artery stenosis demonstrated by an aortography was involved in the development of hypertension in our case prior to surgery. Administration of an alpha-adrenergic blocking agent, phenoxybenzamine, however, produced a definite effect on her hypertension and injection of phentolamine precipitated her blood pressure to nearly normal levels as would be expected in uncomplicated cases of pheochromocytoma. Taken together with a normal renogram and an aortography indicating that the difference in size of both kidneys was not significant, we concluded that renal artery stenosis was not responsible for her high blood

pressure and that her hypertension could be explained solely by a high rate of catecholamines secretion from the tumor. Her postoperative course supports our view.

The preoperative plasma renin activity in this patient was high. This was not induced by the administration of phenoxybenzamine, which has no stimulatory effect on renin secretion in human (see Reference 13 in detail). Similarly, high plasma renin activity could not be attributed to a mild sodium restriction, since the daily rates of urinary sodium excretion ranged from 104 to 211 mEq per day. Serum potassium concentrations as well as its urinary excretion rates, one of the modulators which regulate renin secretion, were also within the normal ranges in this case. Plasma renin activity has been reported to be normal^{18),20)} or elevated^{16),19)-21)} in patients with uncomplicated pheochromocytoma. In latter cases, one of the mechanisms involved has been claimed to be reduction of total blood volume frequently associated with this disease. Elevated plasma renin activity observed in the present case, however, can not be explained simply by this hypothesis, since high levels were sustained after the surgery, when total blood volume returned to normal. A direct effect of catecholamines on renin secretion, on the other hand, has been suggested as another explanation for high plasma renin activity in patients with pheochromocytoma, although no consensus is obtained at present concerning whether catecholamines possess a stimulatory action on renin release.¹⁴⁾⁻¹⁷⁾ Of considerable interest in this context is the finding of Maebashi *et al.*¹⁶⁾ They found that urinary excretion rate of norepinephrine, not epinephrine, in their case of pheochromocytoma could be clearly correlated to the elevation of plasma renin activity. Based on their observation, the preponderance of serum norepinephrine compared to epinephrine may explain the high plasma renin activity in our case. The fact that plasma renin activity was sustained to be high as long as 9 months after the surgery again does not support this concept. Coupled with the facts that no stenosis was demonstrated in renal artery by the aortography performed 14 months after the operation and that postoperative high plasma renin activity was gradually declining to upper normal levels, it might be likely that renal artery stenosis was responsible for the elevation of plasma renin activity in this patient. If this is the case, the explanation for the protracted high renin activity following the surgery may be obscure.

Finally, the localization of pheochromocytoma was determined in this case by the estimation of catecholamines concentrations in blood samples collected by the caval vein catheterization. Concentrations of norepinephrine in samples from left renal vein showed a definitely high level, and the surgery confirmed a solitary pheochromocytoma from the left adrenal gland. When

radiological examinations are not successful in localizing a poorly vasculized tumor as in this case, this approach would be of potential diagnostic value as suggested by von Euler and Ström.²²⁾

ACKNOWLEDGEMENTS

We are indebted to Dr. Y. Ino, Tokyo Second National Hospital for providing us with the clinical data of this patient during her admission in their hospital. And also we are indebted to Professor A. Tasaka and his associates, Department of Radiology of our hospital for performing the angiographies and to Professor H. Takayasu and his associates, Department of Urology of our hospital for surgical treatment.

REFERENCES

1. Rosenheim ML, Ross EJ, Wrong OM, Hodson CJ, Davis DR, Smith JF: Unilateral renal ischemia due to compression of a renal artery by a pheochromocytoma. *Am J Med* **34**: 735, 1963
2. Garret HE, Scott R, Jr, Howell JF, DeBakey ME: Pheochromocytoma and renal artery stenosis. *Arch Surg* **90**: 97, 1965
3. Staube KR, Hodges CV: Pheochromocytoma causing renal hypertension. *Am J Roentgenol* **98**: 222, 1966
4. Weber AL, Janower ML, Griscon NT: Radiologic and clinical evaluation of pheochromocytoma in children: Report of 6 cases. *Radiology* **88**: 117, 1967
5. Sato T, Sakamoto S, Macbashi M, Suzuki C, Furuyama T, Yoshinaga K, Sudo K: Hypertension due to combination of pheochromocytoma and unilateral renal ischemia by tumor compression. *Jap Heart J* **8**: 202, 1967
6. Heberer G, Engelking R, Eigler FW: Diagnostische und therapeutische Besonderheiten bei einigen Hochdruckkranken mit Nierenarterienstenosen. *Deutsche Med Wschr* **92**: 581, 1967
7. Kerzner MS, Reeves JA, DeNyse D, Claunch BC: Pheochromocytoma with renal artery compression in an identical twin. *Arch Intern Med* **121**: 91, 1968
8. Weidmann P, Siegenthaler W, Zeigler WH, Sulser H, Endres P, Werning C: Hypertension associated with tumors adjacent to renal arteries. *Am J Med* **47**: 528, 1969
9. Van Way CW, III, Michelakis AM, Alper BJ, Hutchenson JK, Rhamy RK, Scott WH, Jr: Renal vein renin studies in a patient with renal hilar pheochromocytoma and renal artery stenosis. *Ann Surg* **172**: 212, 1970.
10. McBride JW, Fitz A: Renal artery stenosis, pheochromocytoma and erythrocytosis. *Am J Med* **51**: 403, 1971
11. Naidich TP, Sprayregen S, Goldman AG, Siegelman SS: Renal artery alterations associated with pheochromocytoma. *Angiology* **23**: 488, 1972
12. Page LB, Roth SI: Case records of the Massachusetts General Hospital: Recurrent hypertension in a 13-year-old girl four years after excision of a pheochromocytoma. *New Engl J Med* **288**: 1010, 1973
13. Michelakis AM, McAllister RG: The effect of chronic adrenergic receptor blockade of plasma renin activity. *J Clin Endocrinol Metab* **34**: 386, 1972
14. Vander AJ: Effect of catecholamines and the renal nerves on renin secretion in anesthetized dogs. *Am J Physiol* **209**: 695, 1965
15. Wathen RL, Kingsbury WS, Stouder DA, Schneider EG, Rostorfer HH: Effects of infusion

- of catecholamines and angiotensin II on renin release in anesthetized dogs. *Am J Physiol* **209**: 1012, 1965
16. Maebashi M, Miura Y, Yoshinaga K, Sato K: Plasma renin activity in pheochromocytoma. *Jap Circulat J* **32**: 1427, 1968
 17. Ueda H, Yasuda H, Takabatake Y, Iizuka M, Iizuka T, Ihori M, Sakamoto Y: Observations on the mechanism of renin release by catecholamines. *Circulat Res* **26-27**: II-195, 1970
 18. Brown JJ, Davies DL, Lever AF, Robertson JIS: Plasma renin concentration in human hypertension II: Renin in relation to aetiology. *Brit Med J* **2**: 1215, 1965
 19. Mannhart M, Ludin H, Veyrat R, Zieger WH: Secondary hyperaldosteronism caused by cervical pheochromocytoma cured by ablation of the tumor. *Helvetica Medica Acta* **35**: 479, 1969/70
 20. Werning C, Zieger WH, Baumann K, Endres P, Gysling E, Weidmann P, Siegenthaler W: Die Plasma-Renin-Aktivität beim Phäochromozytom. *Deutsche Med Wschr* **95**: 117, 1970
 21. Herrison TS, Birbari A, Seaton JF: Malignant hypertension in pheochromocytoma: Correlation with plasma renin activity. *Johns Hopkins Med J* **130**: 329, 1972
 22. von Eulerus, Ström G: Present status of diagnosis and treatment of pheochromocytoma. *Circulation* **15**: 5, 1957