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JUXTAGLOMERULAR CELL TUMOR OF THE KIDNEY

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ABSTRACT

A juxtaglomerular cell tumor (JGCT) was found in a 40 year old woman. For 5 years she had mild hypertension, responding to classical anti-hypertensive treatment, then she became severely hypertensive. Two renal angiographies and a CT scan were reported as normal. A second CT scan and third selective renal angiography were diagnostic, associated with lateralization of renin in renal vein measurement. Light, electron microscopy and immunohistochemistry of the resected tumor confirmed the diagnosis of renin-secreting juxtaglomerular cell tumor of the kidney.

INTRODUCTION

Renin-secreting tumors of the kidney represent a curable cause of severe hypertension. After the first case described by Robertson in 1967 (1), 40 other cases have been reported. (2-11).

The diagnosis is difficult to make as these tumors are very small in size and the organ-imaging techniques often overlook them. Therefore the apparent low frequency of this disease may be an underestimation. Since hypertension is completely relieved by the surgical excision of the tumor, it is very important to recognize its etiology. Accurate description of newly presenting JGCT cell tumors is important to improve diagnostic courses.

A renal JGCT was diagnosed in a 40 year old woman whose hypertensive state was controlled for years with conventional anti-hypertensive treatment.

CASE REPORT

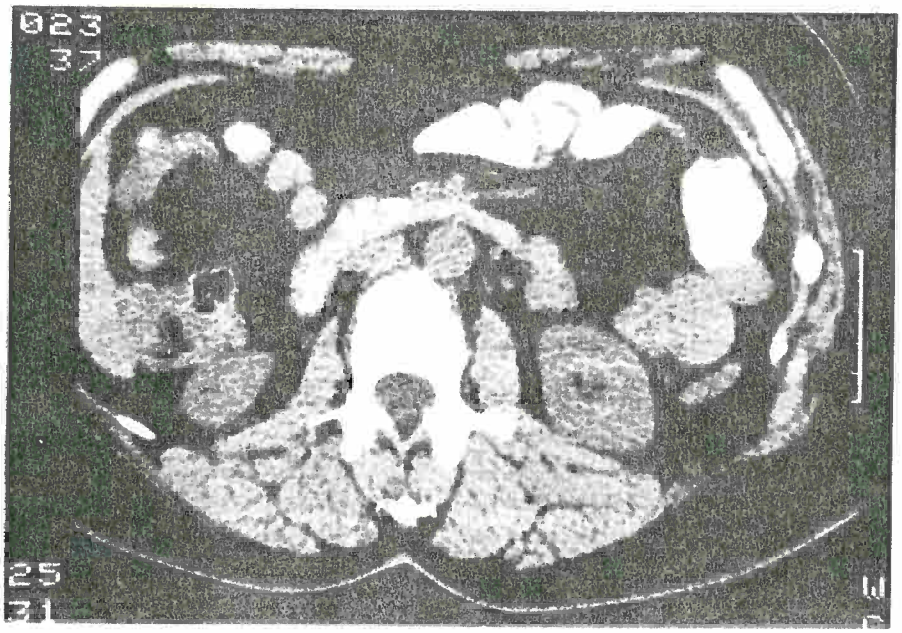
G.C. a 40 year old woman was admitted to our Department in April 1989 for the first time, for severe hypertension. For seven years before admittance to our Department she had attended and had been treated in other Medical Units for hypertension.

Her family history showed no signs of hypertension. Before being hypertensive she had had three pregnancies with normal deliveries. She had also had hemithyroidectomy for nodular goitre and cholecystectomy.

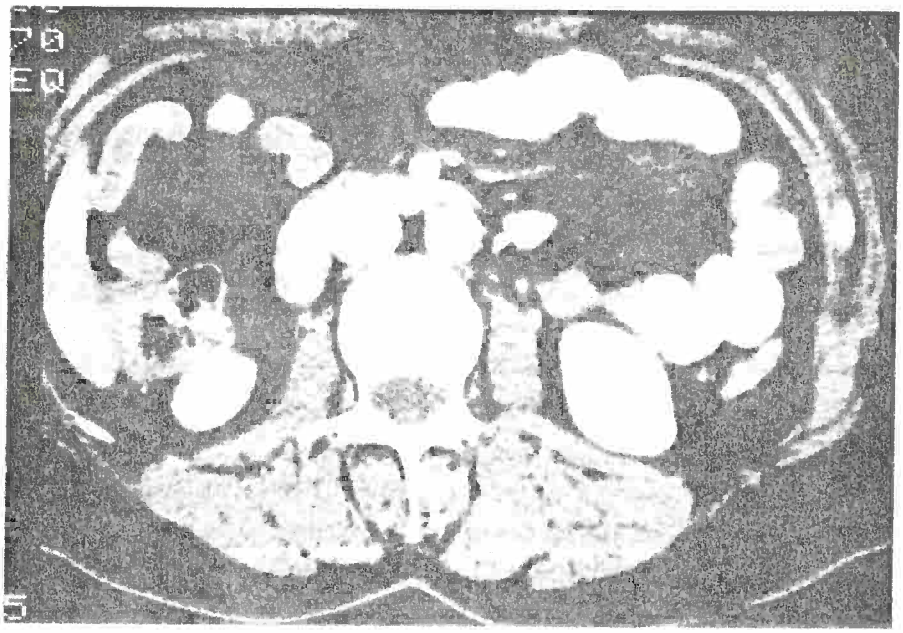
She was found hypertensive when she was 33 year old. At hypertension discovery - before treatment - plasma renin activity (PRA) on recumbency was slightly increased (7.5 ng/ml/h) and serum potassium was at the lower normal limit (3.9 mmol/l). For 5 years arterial blood pressure was controlled with spironolactone (200 mg/day). Then arterial blood pressure increased and she had three hypertensive emergencies (diastolic blood pressure ranging from 120 to 160 mmHg, systolic

from 210 to 260 mm Hg) requiring admission to medical departments. At admission she had severe hypokalemia (2 mmol/l) associated with metabolic alkalosis. Three days after discontinuing anti-hypertensive treatment with enalapril (60 mg\day) and clonidine (450 mg\day), basal PRA (supine and on unrestricted sodium diet) was elevated (37 ng/ml/h) (reported normal values = 0.2-2.7 ng/ml/h) and did not lateralize on renal venous measurements. After volume expansion with saline solution and assumption of the upright posture, PRA decreased to 18 ng/ml/h and 20 ng/ml/h. Plasma aldosterone after overnight recumbency was 250 pg/ml (reported normal range = 12-150 pg/ml) and increased to 476 pg/ml after 2 hour upright posture. Renal angiography , repeated twice, as well as computerized tomography of the kidneys and intravenous pyelography were reported as normal. Blood pressure was elevated (diastolic blood pressure ranging from 100 to 130 mm Hg) despite treatment with enalapril 80 mg/day, nadolol 80 mg/day, clonidine 0.150 mg/day and spironolactone 200 mg/day.

The patient was admitted to our Department in April 1989 for the first time. Physical examination was normal except for the elevated blood pressure (220/120 mmHg). Renal function, serum and urinary electrolytes were in the normal limits: serum urea = 5.7 mmol/l, serum creatinine = 62 umol/l, serum potassium = 4.5 mmol/l, serum sodium = 137 mmol/l, urinary sodium excretion = 120 mmol/day, normal urine analysis. Glomerular filtration rate evaluated by inulin clearance was 118 ml/min. Separate glomerular filtration rate determined with 99 Tc DTPA was 51 ml/min for the left and 49 ml/min for the right kidney. Renal plasma flow (para-amino-hyppuric acid clearance) was 419 ml/min. Twenty four hour urinary catecholamine excretion was normal (23 ug).



(a)



(b)

Fig. 1 CT images of the lower pole of the right kidney (4 mm thick, contiguous slices). Precontrast scan (a): normal parenchymal densitometry, no cists. Postcontrast scan (b) reveals a small, round shape, solid hypodense mass.

During therapy with enalapril alone (60 mg/day) diastolic blood pressure ranged from 100 to 140 mmHg and basal (supine and on unrestricted sodium diet) PRA was 70.7 ng/ml/3h after recumbency and increased to 93.2 ng/ml/3h in upright posture. Plasma aldosterone was moderately elevated (17.6 ng/dl; normal values = 4-12 ng/dl) as well as 24 hour urinary aldosterone (18.1 ug; normal values = 3-12 ug/24 h). Fundus oculi showed grade II hypertensive changes while ECG was normal.

Computerized renal tomography revealed an area of slightly reduced density measuring 1.3 x 1.1 cm in diameter in the lower pole of the right kidney (Fig 1). Nuclear magnetic resonance as well as ultrasound examination of the kidney, however, did not confirm this image.

Anti-hypertensive treatment was discontinued 4 days before repeating renal venous catheterization and angiography. Sodium intake was not restricted during all the hospitalization period. Renal venous renin ratio lateralized to right (right kidney PRA = 145 ng/ml/3h, left kidney = 72 ng/ml/3h, low inferior vena cava = 78 ng/ml/3h, peripheral = 70 ng/ml/3h). On selective renal arteriograms a small hypovascular area was seen in the inferior pole of the right kidney (Fig. 2), confirming the computerized tomography image. The right kidney had two arteries, one perfusing the superior two thirds of the kidney, the other the inferior polar region. The nephrographic phase suggested a slow and partially thrombosed neovascularization of the tumor.

A new renal vein sampling was done in July 1989, while on therapy with enalapril 20 mg/day, clonidine 450 mg/day, amiloride 5 mg/day and hydrochlorothiazide 50 mg/day. Right renal PRA was 183/ng/ml/3h, left PRA 80.4 ng/ml/3h, inferior vena cava PRA 83.5 ng/ml/3h.

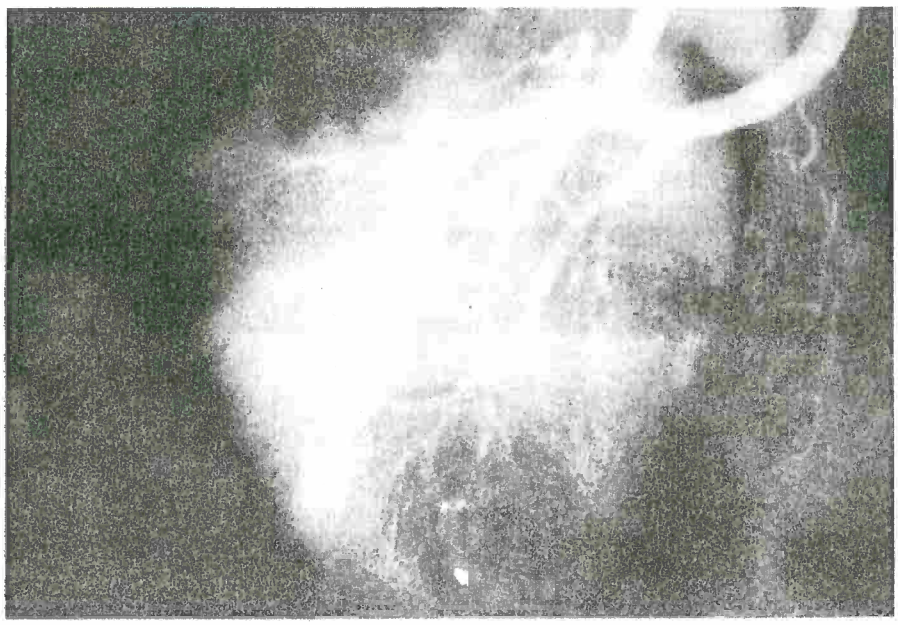


Fig. 2 Selective arteriography of lower right renal artery (x3 magnification, 0.1 x 0.1 mm focal spot) demonstrates in the early arteriographic phase a round, well defined, hypovascular area (a); a tortuous and large interlobular artery reaches the outer cortex (arrow) suggesting vascular neoformation. In the nephrographic phase (b) small areas of contrast stain (arrow) are evident inside the parenchymal "defect", confirming the presence of low flow anarchic circulation.

The patient underwent laparotomy. At surgical exploration the right kidney appeared normal. Inferior polar resection was performed and, on slicing, a well defined nodule of 1 cm x 0.7 cm diameter, was identified.

Light microscopy examination revealed a richly vascularized neoplasm consisting of cells of irregular

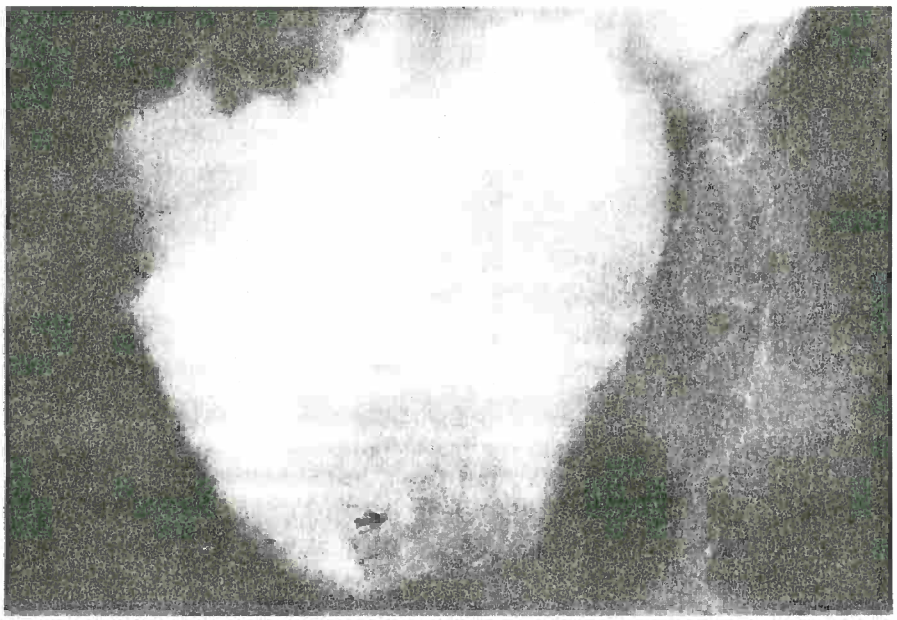
(b) 

Fig. 2 Continued

form, sometimes fusiform, with intracytoplasmic granules and vescicular nuclei. Mitosis were infrequent. The mast cells were prominent.

Electron microscopy revealed a tumor composed of fairly uniform cells with ovoid to elongate nuclei rich in chromatin. Nuclear contours were often indentated. The cytoplasm contained mitochondra, rough-surfaced endoplasmic reticulum and well developed Golgi apparatus. Furthermore, rhomboid granules with crystalline internal fibrillar substance were revealed.

Immunohistochemistry confirmed that these granules contained renin. An in vitro superfusion study was also performed on the removed tumoral tissue and demonstrated a concomitant release of renin and angiotensin I and II (12).

Arterial blood pressure did not fall rapidly to normal after surgery, ranging from 210/120 to 160/100 mmHg in the first days. Enalapril 20 mg/day and kanrenoate 200 mg/day were administered. Blood pressure fell progressively to normal values 15 days after surgery. The patient was discharged on day 16 after surgery with enalapril 10 mg/day and kanrenoate 50 mg/day. One month after surgery blood pressure was 140/90 mm Hg and remained normal after discontinuing anti-hypertensive treatment. PRA, PAC and blood pressure were normal at 6, 12 and 24 months after surgery and she was normotensive without treatment and good in health.

DISCUSSION

As confirmed in our patient, the diagnosis of renin-secreting tumor is not easy because hypertension is not associated with specific clinical symptoms or laboratory data and the tumor is difficult to localize (2,14). This disease usually occurs in patients under thirty years of age (2,14). Our patient, however, was 33 when hypertension manifested and 40 when she underwent surgery. This case was unusual also in that hypertension was mild, not associated with hypokalemia, and controlled with spironolactone for several years. The initial treatment with spironolactone was probably not appropriate for the etiology of the disease and may have contributed to stimulate the renin-angiotensin system, at least at the level of the normal JG cell. Spironolactone treatment may have also obscured the initial effect of secondary hyperaldosteronism on potassium balance.
When severe hypertension manifested, however, PRA was

high and was associated with hypokalemia and metabolic alkalosis. At this time renal angiography was mandatory primarily to exclude a renovascular hypertension. Unfortunately, the presence of a renin secreting tumor is difficult to localize on renal angiograms as these tumors are generally very small in size. As in our patient, other cases have been reported in which the patient underwent one or more renal arteriograms before the tumor was localized on a more careful inspection (6,9,13). Similar considerations must be taken into account regarding CT scan of the kidney and nuclear magnetic resonance, which are considered the most useful imaging techniques for visualizing these tumors. In our patient CT scan image was more indicative than that obtained on nuclear magnetic resonance study.

Though a significant unilateral elevation of PRA by renal vein sampling is considered one of the most important diagnostic criteria for JGCT, the lateralization of renin in renal vein measurements do not always provide an unequivocal answer, as demonstrated in our patient's first sampling. Other Authors have reported similar findings, though the reasons are not clear (6,8,9,15,16,17). Treatment with agents blocking the renin-angiotensin axis may obscure renal vein renin measurements. Moreover it has been suggested that most of the tumor blood may be drained by the peripheral vein rather than by the main renal vein. Finally, it may be that the high angiotensin levels affect the vascularization of the tumor.

Renin-secreting tumors may or may not respond to normal modulators of renin secretion (6,9,16,17). In our patient when hypertension became severe, enalapril at the dose of 60 mg/day was not effective.
As documented in other studies (13), pharmacological

blockage of the renin system is not helpful for diagnosis. In our patient enalapril did not affect basal renin levels while PRA responded to volume stimuli (assumption of upright posture and volume expansion).

Morphological findings of the tumor were typical of JGCT. The ultrastructural study confirmed that the structure of the tumoral cells is similar to that of normal renin-producing cells. As reported by Other Authors (6,9,17), another typical characteristic is the presence of mast cells. This finding is still unexplained as mast cells are not present in the normal juxtaglomerular apparatus.

Following removal of the tumor, the blood pressure usually falls rapidly to normal (16). The observation of a slow return of blood pressure to normal values in our patient may be interpreted as indicating the healing of vascular lesions.

The present case confirms the diagnostic difficulties of identifying renin-secreting tumors. The rarity of these tumors may reflect, at least in part, an underestimation of their prevalence due to difficulties in the diagnosis.

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REFERENCES

1. Robertson, R.W., Klidjian, A., Harding, L.K., Walters, G. Hypertension due to a renin-secreting renal tumor. Am J Med 1967; 43: 963-976.

2. Menard, J., Soubrier, F., Bariety, J., Camilleri, J.P., Corvol, P. Primary reninism. In: Hypertension, J. Genest, McGraw Hill, New York, 1983: 1034-1040.

3. Lindop, G.B.M., Stewart, J.A., Moronie, T.T. The immunocytochemical demonstration of renin in a juxtaglomerular cell tumor by light and electron mycroscopy. Histopathology 1983; 7: 421-431.

4. Squirres, J.P., Ulbright, T.M., Deschryver Kreeskmeti, K., Engleman, W. Juxtaglomerular cell tumor of the kidney. Cancer 1984; 53: 516-523.

5. Tetu, B., Totovic, V., Bechtelsheimer, H., Smerid, J. Tumeur renale a secretion de renine. Ann Pathol 1984; 4: 55-59.

6. Baruch, D., Corvol, P., Alhenc-Gelas, F., Dufloux, M.A., Guyenne, T.T., Gaux, J.C., Raynaud, A., Brisset, J.M., Duclos, J.M., Menard, J. Diagnosis and treatment of renin-secreting tumors. Report of three cases. Hypertension 1984; 6: 760-766.

7. Brand, G., Vandongen, R., Berlin, L.J., Matz, L. Juxtaglomerular tumor: diagnostic renal vein measurements obscured by chronic captopril therapy. Aust N Z J Med 1985; 15: 755-757.

8. Dennis, R.L., McDougal, W.S., Glick, A.D., MacDonell, R.C.jr. Juxtaglomerular cell tumor of the kidney. J Urol 1985; 134: 334-338.

9. Handa, N., Fukunaga, R., Yoneda, S., Kimura, K., Kamada, T., Ichikawa, Y., Takaha, M., Sonoda, T., Tokunaga, K., Kuroda, C., Onishi, S. State of systemic hemodynamics in a case of juxtaglomerular cell tumor. Clin Exp Hypertens 1986; A8: 1-19.

10. Hermus, A.R.M.M., Pieters, G.F.F.M., Lamers, A.P.M., Sinals, A.G.H., Hanselaar, A.G.J.M., Van Haelst, U.J.G., Kloppenborg, P.W.C. Hypertension and hypokalemia due to a renin secreting kidney tumor. Neth J Med 1986; 29: 84-91.

11. Remynse, L.C., Begun, F.P., Jacobs, S.C., Lawson, R.K. Juxtaglomerular cell tumor with elevation of serum erythropoietin. J Urol 1989; 142: 1560-1562.

12. Fallo, F., D'Agostino, D., Armanini, D., Caregaro, L., Mantero, F. Concomitant release of renin, angiotensin I and angiotensin II during superfusion of human juxtaglomerular cells tumor. Am J Hypertension 1992; 5: 566-569.

13. Gordon, R.D., Tunny, T.J., Klemm, S.A., Finn, W.L., Hawkins, P.J., Hunyor, S. J., Norris, J.J. A renin-secreting tumor sensitive to changes in central blood volume (presumably via sympathetics) but not to circulating angiotensin II. Clin Exp Pharmacol Physiol 1990; 17: 185-189.

14. Corvol, P., Pinet, F., Galen, F.X., Plouin, P.F., Chatellier, G., Pagny, J.Y., Corvol, M.T., Menard, J.

Seven lessons from seven renin secreting tumors. Kidney Int 1988; 25(s): 38-44.

15. Lam, A.S.C., Bedard, Y.C., Buckspan, M.B., Logan, A.C., Steinhardt, M.I. Surgically curable hypertension associated with reninoma. J Urol 1982; 128: 572-577.

16. Lindop G.B.M., Leckie B.J., Mimran A. Reninsecreting tumors. In: The renin-angiotensin system. Robertson J.I.S., ed. G.M. Nicholls Gower Medical Publishing, London 1992.

17. Camilleri, J.P., Hinglais, N., Bruneval, P., Bariety, J., Tricottet, V., Rouchon, M., Mancilla-Jimenez, R., Corvol, P., Menard, J. Renin storage and cell differentiation in Juxtaglomerular cell tumors. Hum Pathol 1984; 15: 1069-1079.