

A patient with a juxtaglomerular cell tumor with histological vascular invasion

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SUMMARY

Background A 51-year-old woman was referred to the Hypertension Clinic of L'Hôtel-Dieu de Québec Hospital, University of Québec Hospital Centre, with hypertension. Her hypertension had been evolving for approximately 30 years and was refractory to maximum doses of four antihypertensive agents. Routine blood testing revealed mild hypokalemia.

Investigations Physical examination, urine and blood analyses including measurement of renin and aldosterone levels, echocardiography, funduscopy, abdominal–pelvis CT scan and histopathology studies.

Diagnosis Juxtaglomerular cell tumor with vascular invasion.

Management Radical nephrectomy, and follow-up visits to monitor blood pressure and renin levels.

KEYWORDS aldosterone, hypokalemia, renin, reninoma, resistant hypertension

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe clinical features of juxtaglomerular tumor or reninoma.
- 2 Describe the differential diagnosis of juxtaglomerular tumor.
- 3 Identify the most likely complications of juxtaglomerular tumors.
- 4 Describe the most appropriate treatment for benign reninomas.
- 5 List clinical features that indicate that a reninoma may not be benign.

Competing interests

The authors, the Locum Journal Editor C Harman and the CME questions author D Lie declared no competing interests.

THE CASE

A 51-year-old white woman was referred to the Hypertension Clinic of L'Hôtel-Dieu de Québec Hospital, University of Québec Hospital Centre, with hypertension (160/100 mmHg) despite treatment with the maximum doses of four antihypertensive agents (irbesartan 300 mg, nifedipine gastrointestinal therapeutic system 60 mg, atenolol 100 mg and hydrochlorothiazide 12.5 mg). The patient was otherwise asymptomatic. She had first been diagnosed with hypertension when aged in her twenties and had been started on antihypertensive treatment with the thiazide diuretic hydrochlorothiazide. She had had one successful pregnancy, during which her high blood pressure had required her to continue on her antihypertensive treatment.

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Received 7 April 2008 Accepted 4 June 2008

www.nature.com/clinicalpractice
doi:10.1038/ncpneph0890

At the age of 39 years, the patient had undergone her first full investigation for uncontrolled hypertension (her blood pressure at that time was 170/110 mmHg). Serum levels of potassium, calcium, lipids and thyroid hormone were normal, and urinalysis findings and levels of urinary catecholamines were normal. Abdominal ultrasonography showed that the patient's kidneys were normal. Renal angiography was also normal. On the basis of these findings, the patient was diagnosed with essential hypertension. Her elevated blood pressure, however, remained difficult to control over the following years and she required progressive adjustments of her antihypertensive medications. At the age of 51 years, she was, therefore, referred for the present investigation.

At the hypertension clinic, physical examination revealed a blood pressure of 146/92 mmHg despite continued treatment with maximum doses of all four of the patient's antihypertensive medications. Findings from cardiac, pulmonary and abdominal examinations were unremarkable. Fundoscopy revealed grade II changes by the Keith–Wagener–Barker classification of hypertensive retinopathy (retinal arteriole narrowing and arteriovenous nicking). Echocardiography revealed a slightly increased left ventricular mass but normal systolic and diastolic function. Urinalysis findings were normal. The only notable abnormality revealed by routine blood testing was slight hypokalemia (serum potassium level 3.4 mmol/l; reference range 3.5–5.3 mmol/l). The patient's morning plasma aldosterone concentration was normal (0.22 nmol/l; [morning] reference range 0.08–0.45 nmol/l), but her plasma active renin concentration was extremely high (68 pmol/l [2,800 ng/l] with a two-site immunometric assay, Renin III Generation; Schering–CIS bio international, Gif sur Yvette, France; reference range 0.01–0.97 pmol/l [4–40 ng/l]; cross-reactivity with prorenin 0–1.8%) and there was a very low aldosterone:renin ratio (0.08 pmol/ng; reference value for healthy individuals and patients with essential hypertension <100 pmol/ng). Nonstimulated renal vein sampling revealed slightly lateralized plasma renin concentrations in the right kidney (right renal vein: 57.4 pmol/l [2,364 ng/l]; left renal vein: 43.2 pmol/l [1,776 ng/l]; and inferior vena cava: 59.5 pmol/l [2,450 ng/l]). An abdominal–pelvis CT scan showed that there was a large heterogeneous solid mass (9.8 × 7.3 × 8.5 cm)

located at the superior pole of the right kidney, compatible with a renal cell carcinoma. There were no signs of local invasion or metastasis. Given the size of the tumor, its radiological features and the fact that some renal neoplasms have been reported to produce renin, the most likely preoperative diagnosis was a renal cell carcinoma. The patient therefore underwent a radical right nephrectomy.

Figure 1 shows a macroscopic image of the patient's nephrectomized right kidney, including the tumor. The tumor was well delineated and showed soft black hemorrhagic and solid yellow areas. Viewed by conventional light microscopy, the tumor was again well delineated and the tumor tissue was made up of sheets of polygonal to ovoid cells with regular nuclei, distinct cell borders, moderately abundant granular eosinophilic cytoplasm, little pleomorphism and low mitotic activity (Figure 2). Granules stained positively with periodic acid–Schiff and toluidine blue stains. Numerous hemangiopericytoma-like vessels were focally present. Surprisingly, the tumor was clearly extending into the lumen of a vein (Figure 3). Mitotic activity of the tumor cells was low. Tumor cells were immunoreactive for renin (P Bruneval, Georges Pompidou European Hospital, Paris, France; dilution 1:1,000; Figure 4), actin (Dako, Glostrup, Denmark; dilution 1:50), vimentin (Dako; dilution 1:10) and CD34 (Becton, Dickinson & Co. Biosciences, San José, CA, USA; dilution 1:50), as is characteristic of juxtaglomerular cell tumors. Abundant rough endoplasmic reticulum, and angulated, rhomboid renin protogranules were seen on ultrastructural examination of the tumor tissue.

Three days after the nephrectomy, the patient's blood pressure (120/80 mmHg) and plasma renin concentrations (0.12 pmol/l [5 ng/l]) were normal. At 2-year and 3-year follow-up visits after the nephrectomy, the patient's blood pressure (128/82 mmHg and 130/80 mmHg, respectively), serum potassium values (4.1 mmol/l and 4.2 mmol/l, respectively), plasma renin concentrations (0.10 pmol/l [4 ng/l] at both visits) and plasma aldosterone values (0.14 nmol/l and 0.16 nmol/l) had remained normal without use of antihypertensive medications.

DISCUSSION OF DIAGNOSIS

The case reported here is one of a juxtaglomerular cell tumor, or reninoma, showing malignant features with vascular invasion.

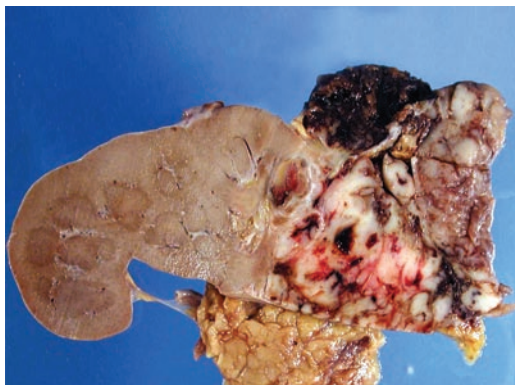


Figure 1 Macroscopic image of the nephrectomized right kidney, showing the tumor at the superior pole. The tumor was solid, heterogeneous and had hemorrhagic areas.

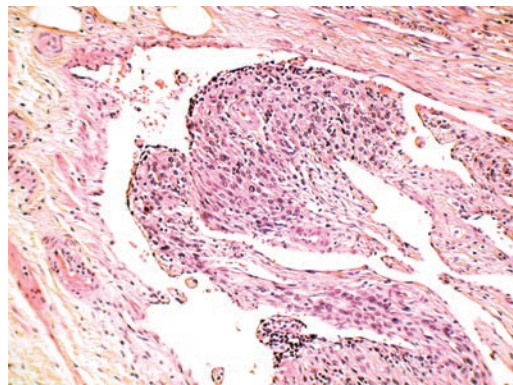


Figure 3 Photomicrograph of tumor tissue (original magnification $\times 100$; hematoxylin–eosin stain) showing that the tumor extended into a venous lumen.

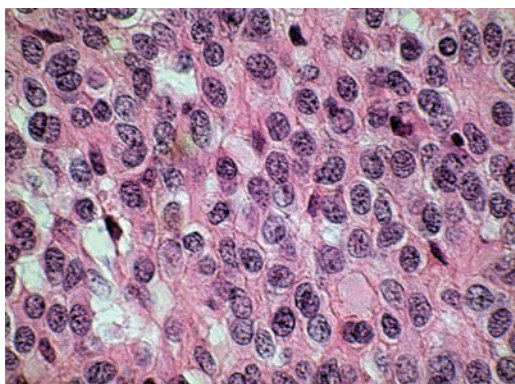


Figure 2 Photomicrograph of tumor tissue (original magnification $\times 400$; hematoxylin–eosin stain). Tumor cells were polygonal to ovoid in shape with regular nuclei, moderately abundant granular eosinophilic cytoplasm, distinct cell borders, little pleomorphism and low mitotic activity.

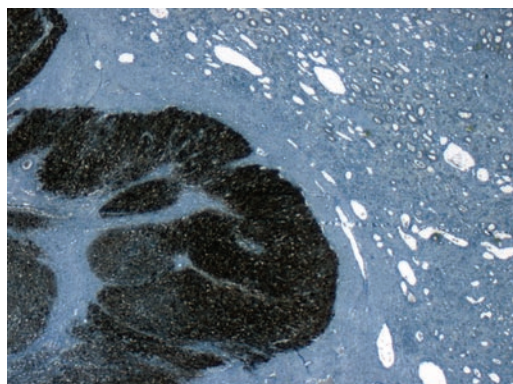


Figure 4 Photomicrograph of tumor tissue (original magnification $\times 25$; anti-renin antibody) showing that tumor cells were immunoreactive for renin.

Primary reninism is a very rare cause of secondary hypertension.¹ More than 80 cases of juxtaglomerular cell tumors have been described since the first case reported by Robertson *et al.* in 1967.² Juxtaglomerular cell tumors are seen more frequently in women than in men, and they usually occur during adolescence or early adulthood.¹ Juxtaglomerular cell tumors are commonly associated with hypertension, secondary aldosteronism and hypokalemia.¹ Although both renal^{3,4} and extrarenal^{5–10} renin-secreting neoplasms have been reported, such tumors usually arise in the kidney from the juxtaglomerular apparatus. Diagnosis of juxtaglomerular cell

tumors is not always easy, and the tumors can be small and distally located in the renal cortex. Radiological images of juxtaglomerular cell tumors can be easily confused with those of cystic and other benign kidney lesions.^{1,11} In the present case, plasma renin concentrations were not clearly lateralized on the tumor side (right:left renal vein ratio 1.33). The literature, however, reports the presence of lateralization by surgical findings in only 26 out of 45 cases in which renal renin sampling was performed.¹ In a case described by Wong *et al.* in 2008,¹ renin lateralization was demonstrated solely through use of segmental renal catheterization following administration of an angiotensin-converting-enzyme inhibitor. In the case presented here, a large dissociation between the concentration of plasma renin and

that of plasma aldosterone was also observed. A similar dissociation has been observed in renovascular hypertension;¹² indeed, not all cases of renal artery stenosis are accompanied by hyperaldosteronism¹²—not even those induced experimentally.¹³

A juxtaglomerular cell tumor is usually a surgically curable cause of hypertension,¹⁴ and this tumor type has usually been considered benign. The case presented here and a report by Duan *et al.*¹⁵ suggest, however, that there is potential for vessel invasion and metastasis with such tumors.

An atypical feature of the present case was the discovery that the tumor had a largest diameter of 9.8 cm—much larger than would be expected with a reninoma (which tumor types usually have a largest diameter of 2–3 cm). This presentation is consistent with that of a tumor that has been growing for many years. The patient was 51 years old at the time of diagnosis, whereas the typical patient is diagnosed with reninoma at between 15 and 35 years of age. The fact that the patient presented here had been hypertensive for 30 years and was completely cured after surgery indicates that the renin overproduction by the tumor was the main contributor to her hypertension. Although the findings of the first investigations when the patient was 39 years old, including those of a renal arteriogram, were negative, plasma renin and aldosterone levels were not measured at that time. The patient's tumor had probably been present since the beginning of her hypertension and been missed on the first renal arteriogram. The atypical features of this case (older age and an unusually large tumor) were also observed in the patient with a metastatic juxtaglomerular cell tumor reported by Duan *et al.*¹⁵

The most unexpected histological observation in the patient described here was the presence of a focus of vascular invasion. That was, however, the only finding suggestive of potential malignancy. The cell morphology was otherwise typical of a benign reninoma. These findings suggest that juxtaglomerular cell tumors might have the capacity to invade vessels and to disseminate throughout the body, despite displaying benign histological features. The same evolution has been described in other endocrine tumors such as pheochromocytoma, in which histological features cannot be used to reliably distinguish malignant from benign tumors.¹⁶

The presence of vascular invasion in such tumors is not, however, a definitive criterion for malignancy. Indeed, Thompson *et al.*¹⁷ reported two cases of benign pheochromocytoma with vascular invasion.

To our knowledge, the present report is the first case of 'benign' reninoma showing histological vascular invasion.

TREATMENT AND MANAGEMENT

Most of the time, juxtaglomerular cell tumors are superficial and can easily be removed laparoscopically by nephron-sparing partial nephrectomy.¹ Radical nephrectomy should be considered for a presumed reninoma that is located deep in the renal parenchyma or one that is very large with suspicion of malignancy, as in the present case. Given the histological vascular invasion by the tumor, the patient presented here should be followed up annually for measurement of blood pressure and renin levels to enable detection of recurrence and metastases of the juxtaglomerular cell tumor.

CONCLUSIONS

Although juxtaglomerular cell tumors have always been considered benign, the present case, together with a recent report of a metastatic juxtaglomerular cell tumor,¹⁵ challenge this consensus. On the basis of these reports, clinical signs of potential malignancy in juxtaglomerular cell tumors include histological vascular invasion, a large tumor size, and/or relatively advanced patient age. Patients with such signs should have annual follow-up visits so that recurrence of hypertension and/or hyperreninemia is detected.

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Acknowledgments

Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests

The authors declared no competing interests.

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