Case Report

Malignant Hypertension Due to a Large Reninoma: A Case Report

Chantanij Leemingsawat MD*,
Nuntakorn Thongtang MD*

**Division of Endocrinology and Metabolism, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

A thirty-year-old-man was admitted due to visual loss from malignant hypertension. Hypokalemia and urinary potassium loss were found. Plasma renin activity (PRA) and aldosterone were investigated and found to be elevated compatible with secondary hyperaldosteronism. A computed tomography of the abdomen showed a 11.7 x 11.3 x 12 cm ill-defined, non-homogeneous mass at the middle part of right kidney. The preoperative diagnosis was renal cell carcinoma and the patient underwent right radical nephrectomy. Following nephrectomy, plasma PRA and plasma aldosterone levels declined and serum potassium level returned to normal.

A reninoma is a rare benign renal neoplasm arising from juxtaglomerular apparatus. The tumor produces an excessive amount of renin resulting in secondary hyperaldosteronism, thereby causing hypertension with hypokalemia. The authors describe a case of reninoma in a young man, who presented with malignant hypertension and the largest reninoma ever reported.

Keywords: *Reninoma, Malignant hypertension, Hyperaldosteronism*

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A thirty-year-old-man presented with blurred vision for 20 days. He had been diagnosed with hypertension at a local hospital seven days ago with presenting blood pressure of 200/100 mmHg. Hydrochlorothiazide and amlodipine had been prescribed. He denied a history of headache, nausea, vomiting, palpitation, and muscle weakness. He had been smoking for 10 years. On examination, his blood pressure was 190/100 mmHg. An ill-defined mass of rubbery consistency about 12 x 6 cm in diameter was palpated at the right upper quadrant of the abdomen. Ophthalmological examination revealed a visual acuity of 20/50 at the right eye and 20/60 at the left eye. The pupils were normally reactive to light both eyes. There were papillary edema, flame-shaped hemorrhage and cotton wool spot in both retinas. At presentation, he had renal insufficiency; his creatinine level was 1.7 mg/dl. Serum electrolyte showed hypokalemia and metabolic alkalosis (sodium 133 mmol/l, potassium 2.3 mmol/l, chloride 89 mmol/l, bicarbonate 33 mmol/l). A urinalysis showed moderate proteinuria without uninary sediment. Urinary vanillylmandelic acid level was 5.9 mg/day (normal 1.5-10 mg/day). EKG showed left ventricular hypertrophy indicating long standing hypertension.

He was diagnosed with malignant hypertension and was admitted for urgent control of blood pressure. The patient was treated initially with intravenous nicardipine, and hydrochlorothiazide was discontinued due to hypokalemia. Nifedipine GITS 120 mg/day, hydralazine 300 mg/day and doxazosin 2 mg/day were required to control his blood pressure. The patient had persistent hypokalemia which necessitated administration of 120 mEq of potassium daily after hydrochlorothiazide was discontinued. Morning plasma aldosterone level and plasma renin activity were assessed after correction of hypokalemia. The plasma renin activity was 12 ng/ml/hr (normal upright 1.5-5.7 ng/ml/hr). Plasma aldosterone level was 102 ng/dl (normal upright 3.5-35 ng/dl). These indicated a state of secondary hyperaldosteronism.

A computed tomography of the abdomen showed a well-defined inhomogeneous nodular enhancing mass with a necrotic portion at the middle

Correspondence to:
Thongtang N, Division of Endocrinology and Metabolism, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: 0-2419-7000
E-mail: sinuntakorn@mahidol.ac.th

part of right kidney measuring about 11.7 x 11.3 x 12 cm (Fig. 1). Differential diagnoses of the radiographic feature were renal cell carcinoma, mesenchymal cell tumor, and reninoma. Renal artery catheterization was performed and showed no evidence of renal artery stenosis. The patient underwent right radical nephrectomy. During an operation, a 12 x 12 x 10 yellowish mass was found at the middle part of right kidney. The rest of the kidney parenchyma appeared normal. There was no lymphadenopathy. Liver surface appeared normal.

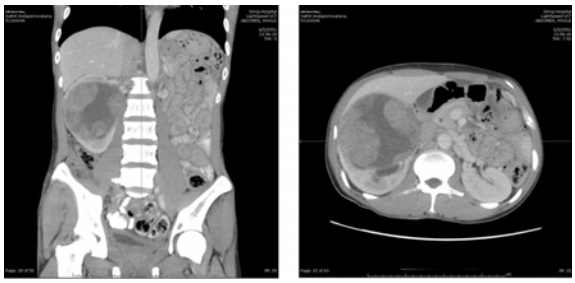

Fig. 1 Abdominal CT scan shows a 11.7 x 11.3 x 12 cm tumor in the middle pole of right kidney

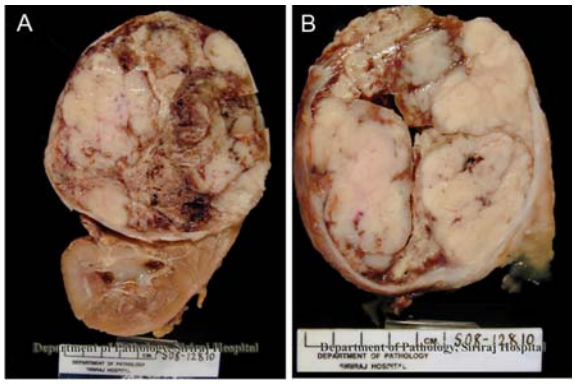

Fig. 2 Gross examination demonstrated a large well-encapsulated tumor at the middle part of right kidney (A) Cut surface of the mass shows non-homogenous light brown tumor with necrosis and hemorrhage (B)

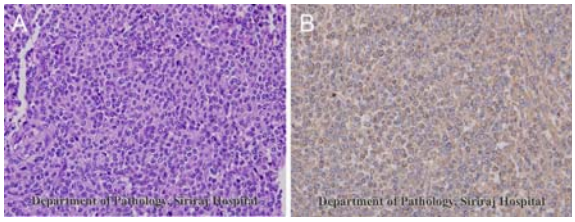

Fig. 3 Histological examination revealed tumor cells with uniform round to oval nuclei and rare mitotes (A). Tumor cells showed positive immunoreactivity with vimentin (B)

Pathology

Gross examination demonstrated a large well-encapsulated mass, measuring 11.5 x 11 x 8 cm at the middle part of right kidney. Cut surfaces of the mass showed non-homogeneous light brown tissue with massive necrosis and hemorrhage (Fig. 2).

Microscopically, tumor cells had uniform, round to oval nuclei with rare mitoses (Fig. 3). Special stain with renin cannot be performed in Siriraj Hospital. However, the tumor showed positive immunoreactivity with vimentin (Fig. 3) and focally stained with CD34, CD10, and CD99. Immunoreactivity with AE1/AE3, HHF35, 1A4, S100 protien, chromogranin, synaptophysin, and CD45 showed negative stain. These findings were suggestive of juxtaglomerular cell tumor. Electron microscopic examination showed that most of the nuclei of the tumor cells were round to oval shape with perinuclear chromatin. The cytoplasm contained a large number of rough endoplasmic reticulum and a moderate number of mitochrondria. Pleomorphic granules presented with rounded bodies, polygonal in shape, with homogeneous or granular electron-dense content being observed in the cytoplasm. These findings were also compatible with reninoma.

Microscopic examination of non-neoplastic kidney demonstrated segmental sclerosis of 20% glomeruli, global sclerosis of 5-10% glomeruli and some moderate to severe tubular atrophy compatible with focal and segmental glomerulosclerosis (FSGS). The adrenal glands and renal vessels were unremarkable.

Follow-up

After nephrectomy, the patient's blood pressure was 160/90 mmHg and remained elevated. To normalize blood pressure, the patient required nifedipine GITS 120 mg/day and atenolol 100 mg/day. His serum potassium level returned to normal at 4.5 mmol/l without the need for potassium supplementation. His serum creatinine had risen to 3.3 mg/dl and blood urea nitrogen was 30 mg/dl after the surgery. Total blood loss during the operation was estimated to be about 350 ml and there was no intraoperative hypotension.

The patient's morning plasma aldosterone and plasma renin activity were measured at one week after nephrectomy and were found to be normal (Plasma aldosterone 7.32 ng/dl and plasma renin activity 0.1 ng/ml/hr). At 6-months after operation, his serum potassium levels remained normal (serum potassium

4.2 mg/dl) but he still had hypertension (blood pressure 145/89 mmHg). Manidipine 40 mg/day, doxazosin 4 mg/day and methyldopa 250 mg/day were required to control his blood pressure. Proteinuria and renal insufficiency were persistent from long standing hypertension (serum creatinine 2.8 mg/dl). The plasma renin activity was 2.8 ng/ml/hr (normal upright 1.5-5.7 ng/ml/hr) and plasma aldosterone level was 71.8 ng/dl (normal upright 3.5-35 ng/dl). Since plasma aldosterone level was elevated, renal ultrasonography was performed and no mass was found at the right kidney base area. There was no evidence of tumor recurrence up until 3 years after the surgery.

Discussion

Juxtaglomerular cell tumor of the kidney is a rare kidney neoplasm. It was first described by Roberson et al in 1967 and Kihara et al in 1968[1]. Since 1967, there have been 119 reported cases of hypertension due to juxtaglomerular cell tumor[2]. The tumor was typically found in young adults, with a peak incidence in the second and third decades. The mean age at diagnosis was 27 years[3]. Juxtaglomerular cell tumors were seen more frequently in women than in men. The patients commonly presented with severe uncontrolled hypertension, hyperaldoteronism and hypokalemia secondary to renin producing tumor. The mean duration of hypertension was 47 months. Most patients had very high blood pressure and hypertensive end organ damage was common in patient with juxtaglomerular cell tumor. Retinopathy was detected in 24% of the cases and papilledema was found in 6%. Proteinuria, renal insufficiency and left ventricular hypertrophy have been reported in 11%, 3% and 7% of the cases respectively[3]. Almost all patients had hypokalemia or serum potassium levels in the lower part of the normal range. Hypokalemia was detected at presentation in 81% of the cases. Plasma renin activity levels were 3-70 times above the upper normal limit (mean $\pm$ SD PRA = 12 $\pm$ 11 ng/ml/hr). Plasma aldosterone concentration was normal or elevated[3].

In order to diagnose the etiology of hyperreninism, imaging studies have been used to describe the lesion anatomically[3,4]. Nearly all juxtaglomerular cell tumors were visible on CT imaging. Both MRI and CT scans are highly effective at determining the presence of a juxtaglomerular cell tumor[3]. The diagnosis of juxtaglomerular cell tumors is occasionally difficult because the tumors may be small and located distally in the renal cortex, thus it could be confused with other benign kidney lesions. Determination of plasma renin levels by selective catheterization of the renal vein may help to localize the tumor[5]. Gross appearance of juxtaglomerular cell tumor typically shows a well-circumscribed cortical mass confined to the kidney. The cut surfaces of these neoplasm usually are yellow to tan-gray, with areas of hemorrhage[6]. Microscopically, juxtaglomerular cell tumors are well circumscribed and partially or fully surrounded by a thick fibrous capsule[6]. Although capsular invasion or vascular invasion has been described, this does not correlate with aggressive behavior[5,7]. The tumors are composed of variable size cells with round, oval to spindle-shaped nuclei and variable amounts of lightly eosinophilic cytoplasm. The histological differential diagnosis included hemangiopericytoma, renal cell carcinoma and collecting-duct carcinoma[8].

Because of its rarity, the immunophenotype of juxtaglomerular cell tumor is not entirely clear. Thus far, almost all juxtaglomerular cell tumors examined have shown positivity for renin and several have shown positivity for smooth-muscle actin, vimentin and CD34[3,6,9]. Juxtaglomerular cell tumors do not stain for cytokeratin, chromogranin, synaptophysin, HMB-45, S-100, c-kit, CD31, factor VIII, or desmin[6]. Electron microscopic examination usually revealed the presence of polygonal cells with round to oval nuclei containing dispersed chromatin. The cytoplasm contained abundant rough endoplasmic reticulum and prominent Golgi apparatuses[3,6]. However, the presence of the intracytoplasmic rhomboid crytalline protogranules is considered to be a confirmatory diagnosis of juxtaglomerular cell tumor[6,8].

The present case showed gross and microscopic characteristic features of juxtaglomerular cell tumor. Special stain showed positive vimentin and CD34 which were also found in the other reported cases of juxtaglomerular cell tumor. Although the electron microscopic examination did not find the intracytoplasmic rhomboid crytalline protogranules, other ultrastructure features, including prominent rough endoplasmic reticulum and mitochrodria have been found in the previously reported cases of this tumor. Therefore, the authors pathological findings support the diagnosis of juxtaglomerular cell tumor. From previously reported cases, the tumor size ranged from 0.2-9 cm with a mean diameter of 3 cm[3]. The largest juxtaglomerular cell tumor previously reported by Beaudoin et al in 2008 was 9.8 cm in diameter[5]. This patient's tumor size was 12 x 11 cm, which is the largest reninoma ever reported. Moreover, in the previous report, the patients with large reninoma usually

presented at older ages[5,9], whereas this patient was diagnosed at 30 years of age, which is the youngest patient reported to have a large reninoma.

Juxtaglomerular cell tumors usually locate superficially and can be easily removed by laparoscopic nephron-sparing partial nephrectomy[10,11]. 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. Juxtaglomerular cell tumors have always been considered benign; however, malignant juxtaglomerular cell tumors have been reported[9]. Clinical signs of potential malignant juxtaglomerular cell tumors include histological vascular invasion, a large tumor size, and relatively advanced patient age[5]. Although the pathological study had not found capsular invasion or vascular invasion in the presented case, malignancy is needed to be considered due to a large tumor size. Therefore, his blood pressure and plasma renin activity should be followed up annually.

A juxtaglomerular cell tumor is a rare cause of secondary hypertension which is usually surgically curable[12,13]. Persistent hypertension after surgery had been reported at about 11-27%, probably due to vascular damage induced by prolonged hypertension[3,8,9,14-18]. In the present case, the kidney adjacent to the tumor showed features of focal and segmental glomerulosclerosis (FSGS). He had postoperative proteinuria and renal insufficiency which may reflect longstanding hypertensive damage to the contralateral kidney. It is important to establish the diagnosis early to reduce the risk of developing sustained hypertension and hypertension-related complications.

In summary, we reported a 30-year old patient who had severe hypertension due to a renin-secreting juxtaglomerular cell tumor at his right kidney. The unusual features of our patient include a large tumor that is uncommon in juxtaglomerular cell tumor, and a young age of onset for such a large tumor. His plasma renin activity and serum potassium returned to normal after the surgery.

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Potential conflicts of interest

None.

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รายงานผู้ป่วยความดันโลหิตสูงชนิดร้ายจากเนื้องอก reninoma ขนาดใหญ่

ฉันทนิจ ลี้มิ่งสวัสดิ์, นันทกร ทองแตง

ผู้ป่วยชายอายุสามสิบปีเข้ารับการรักษาตัวในโรงพยาบาลด้วยอาการตามัวเนื่องจากภาวะความดันโลหิตสูง ระดับร้ายแรง (malignant hypertension) ผลการตรวจทางห้องปฏิบัติการพบว่าผู้ป่วยมีระดับโพแทสเซียมในเลือดต่ำและมีโพแทสเซียมรั่วออกทางปัสสาวะ ผู้ป่วยมีระดับการออกฤทธิ์ของเร็นนินและอัลโดสเตอโรนในพลาสมาสูงเข้าได้กับภาวะอัลโดสเตอโรนนิสมทุติยภูมิ (secondary hyperaldosteronism) ผลการถ่ายภาพรังสีโดยคอมพิวเตอร์ (Computerized tomography) ช่องท้องพบก้อนขนาด 11.7 x 11.3 x 12 ซม. ขอบเขตไม่ชัดเจนที่ส่วนกลางของไตขวา ผู้ป่วยได้รับการวินิจฉัยเบื้องต้นเป็นมะเร็งไตและได้รับการผ่าตัด right radical nephrectomy ภายหลังการผ่าตัดระดับการออกฤทธิ์ของเร็นนิน อัลโดสเตอโรนในพลาสมา และโพแทสเซียมในซีรัมกลับสู่ระดับปกติ

เนื้องอก reninoma เป็นเนื้องอกซึ่งเกิดจากเซลล์ juxtaglomerular apparatus พบได้น้อยมาก เนื้องอก reninoma ผลิตสารเร็นนินเป็นปริมาณมากทำให้เกิดภาวะอัลโดสเตอโรนนิสมทุติยภูมิ ทำให้ผู้ป่วยมีความดันโลหิตสูงร่วมกับระดับโพแทสเซียมในเลือดต่ำ รายงานนี้นำเสนอผู้ป่วยชายอายุน้อยซึ่งมาด้วยความดันโลหิตสูงระดับร้ายแรงและมีเนื้องอก reninoma ขนาดใหญ่ที่สุดเท่าที่เคยมีการรายงาน