Perioperative Hypertensive Crisis in Clinically Silent Pheochromocytomas: Report of Four Cases

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Improvements in imaging have resulted in an increase in incidentally discovered adrenal tumors. The adrenal incidentalomas have been identified in at least 2%~3% of patients receiving abdominal computed tomography (CT), and pheochromocytomas are reported to occur in about 5.1%~23.0% of those patients. Only a few case reports of clinically silent pheochromocytomas have been published in the English literature. Herein we present 4 cases of pheochromocytomas as unforeseen adrenal masses on abdominal images. The characteristics of these tumors were that they (1) were noted to have no particular symptoms, (2) were confirmed biochemically and pathologically with immunophenotypic staining, (3) were benign in nature, and (4) produced apparent blood-pressure fluctuations during the operation. Three of these patients underwent a hypertensive crisis during surgery, and antihypertensives were applied transiently for blood pressure control. Two cases suffered from dramatic hypotension after the tumor had been excised, and intravenous fluid expanders and ephedrine were necessary to maintain adequate blood pressure. The above changes in blood pressure had no correlations with the size of the tumors. Although these tumors were clinically silent, they indeed were biologically active. Surgical resection of these tumors was indicated, and the risk of complications, such as hypertensive or hypotensive crises, may be no less than those of other typical tumors. Thus, such tumors should be managed with great caution. *(Chang Gung Med J 2005;28:44-50)*

Key words: adrenal tumor, incidentaloma, pheochromocytoma, hypertensive crisis.

Advances in imaging studies, such as high-resolution ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), have resulted in the incremental perception of otherwise unforeseeable adrenal tumors including pheochromocytomas.[1-3] The prevalence of adrenal masses confirmed on CT scanning for reasons other than suspected adrenal pathology was about 2%~3%.[4,5] Among adrenal incidentalomas, approximately 5.1%~6.5%,[4,5] even up to 23.0%,[2] were proven to be pheochromocytomas, and 10% of adrenal pheochromocytomas acted as adrenal incidentalomas with no clinical symptoms.[5]

Patients with pheochromocytomas account for less than 1% of the population with hypertension. Most of these tumors are symptomatic, but 10%~30% have been reported to be asymptomatic.[6] These clinically silent pheochromocytomas exist without typical symptoms of hypertension, headaches, palpitations, or sweating.

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The following questions were elicited by these atypical silent pheochromocytomas. Do these tumors differ from typical pheochromocytomas that we commonly recognize? What is the chance of a hypertensive crisis in these patients? What kind of treatment protocol should be set up for the pre- and perioperative periods? Herein we present 4 cases of pheochromocytomas as adrenal masses fortuitously detected on abdominal images (Table 1). Dramatic changes in blood pressure were noted with tumor removal.

CASE REPORTS

Case 1

A 50-year-old previously healthy man came to our outpatient department (OPD) for body-weight loss of about 2 kg within 1 month. Abdominal sonography initially located a solid hepatic mass. He had no history of hypertension, Cushingoid appearance, tremors, edema, headaches, palpitations, or dyspnea with a normal level of exercise. At the OPD, his blood pressure (BP) was 126/82 mmHg and heart rate (HR) was 75/min. Abdominal CT and MRI revealed a right-side adrenal tumor, 5 cm in diameter, with central necrosis and soft-tissue density, but no apparent hepatic mass.

The following laboratory data were obtained: sodium of 141.5 meq/l, potassium of 3.65 meq/l, fasting glucose of 229 mg/dl, resting plasma aldosterone concentration of 151 pg/ml, (normal, 30 to 160 pg/ml), plasma renin activity of 1.8 ng/ml/h (normal, 0.15 to 2.33 ng/ml/h), cortisol 16.6 μg/dl (normal, 6 to 23 μg/dl) at 8 a.m. and 5.51 μg/dl (normal, 3 to 14 μg/dl) at 4 p.m., 24-h urine metanephrine of 7277 μg/day (normal, 52 to 341 μg/day), normetanephrine of 1369 μg/day (normal, 88 to 444 μg/day), and 3-methoxytyramine of 474 μg/day (normal, 10 to 296 μg/day).

During a right-side laparoscopic adrenalectomy, the BP and HR greatly varied. The BP once increased to 220/130 mmHg and the HR to 105/min. During surgery, nitroglycerin was administered via a continuous intravenous drip for about 1.5 h (Fig. 1), and hydralazine and labetalol were intermittently used to enhance hypertension control. However, the BP dropped sharply after tumor excision, thus, ephedrine was used to transiently increase it. When the surgery was completed, his BP and HR returned to normal ranges on the next day, and his fasting plasma glucose level was 71 mg/dl. No apparent complications were noted. Pathology confirmed a benign pheochromocytoma.

Case 2

A previously healthy 56-year-old woman had experienced mild upper abdominal pain for 3 days. Abdominal sonography revealed a 4 x 5-cm unanticipated solid adrenal mass. Her past history revealed no hypertension, Cushingoid appearance, tremors,

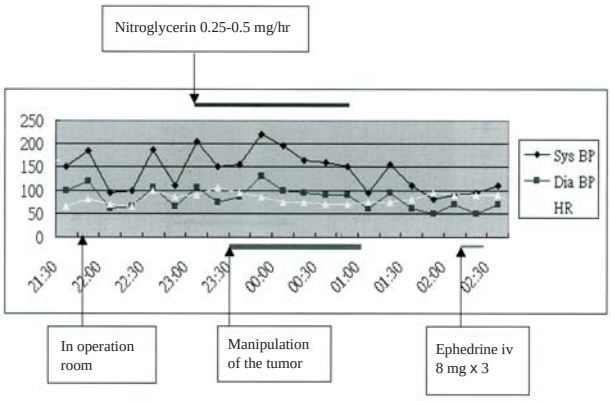

Fig. 1 Vital sign changes during operation in case 1

Table 1. Demographic and Clinical-Pathological Data of the patients with Silent Pheochromocytomas

Case	Gender	Age (years)	Side	preoperative impression	BP at OPD (mmHg)	Highest BP (mmHg) during operation	Tumor size (cm)	Positive immmunohistochemical stain*
1	M	50	R	adrenal tumor, suspect pheochromocytoma	126/82	220/130	7x8x5	CD56.Syn.CG
2	F	56	L	Adrenal tumor	125/75	180/100	5.5x4x3	Syn, CG
3	M	67	R	Adrenal tumor	130/80	205/115	3.5x3.5x2	Xyn. CG.
4	F	40	R	Adrenal tumor, suspect pheochromocytoma	124/80	220/120	5x3x3	CD56. Xyn. CG

Abbreviations: M: male; F: female; R: right; L: left

* Pan-neuroendocrine markers, including chromogranin (CG), synaptophysin (Syn), and CD56.

headaches, or apparent body weight change. At the OPD, her BP was 125/75 mmHg and HR was 85/min. Abdominal MRI revealed a left-side adrenal tumor, 5 cm in diameter (Fig. 2).

The following laboratory results were obtained: sodium of 140.8 meq/l, potassium of 3.27 meq/l, and fasting glucose of 201 mg/dl. During the left-side laparoscopic adrenalectomy, the BP once rose to 180/100 mmHg and the HR to 95/min (Fig. 3). Because no further elevation of BP and HR occurred, no medication was given. No apparent complications were noted. Pathology confirmed a benign pheochromocytoma (Fig. 4).

Case 3

A previously healthy 67-year-old man came to our GI OPD for recent abdominal fullness and hiccups. Abdominal sonography first showed a solid hepatic mass. His past history revealed no hypertension, cushingoid appearance, tremors, edema, headaches, or palpitations. At the OPD, his BP was 130/80 mmHg and HR was 78/min. Abdominal CT sensed a right-side adrenal tumor, 3 cm in diameter,

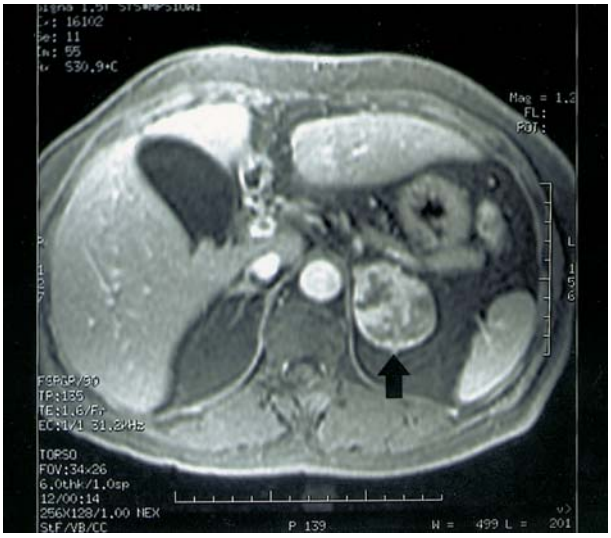

Fig. 2 Abdominal MRI with intravenous Gd-DTPA enhancement. A mass measuring about 5 cm in diameterwith a central necrosis and soft-tissue density is in left adrenal region. This lesion reveals intermediate signal intensity in TA1WI and heterogeneously high signal intensity in T2WI. In the chemical shift imaging, no significent chang eof the signal intensity is identified. After administration of Gd-DTPA, early but heterogeneous and prolonged enhancement is identified. No definite para-aortic lymphadenopathy is identified.

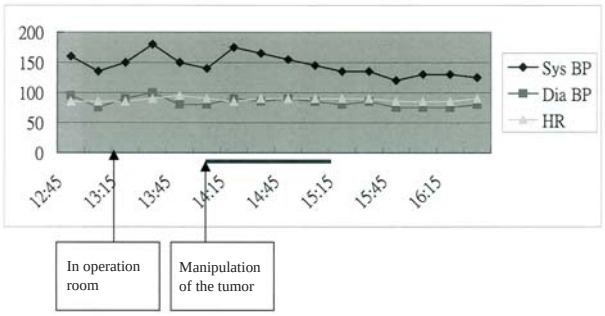

Fig. 3 Vital sign changes during operation in case 1

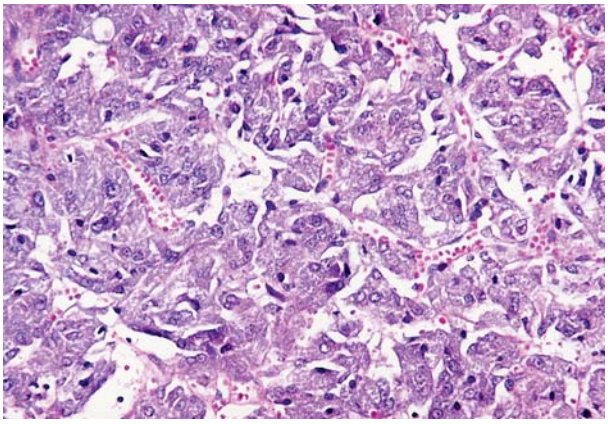

Fig. 4 Histology of the resectedtumor in case 2.the tumor cells are polygonal with finely granular and eosinophilic cytoplasm. Nest of large uniform cells with rounded nucleoli arranging in Zellballen pattern is noted. The nuclei have a salt and pepper chromatin, which is characteristic of neuroendocrine tumors.Also of noted is the relative lack of mitotic activity and nuclear pleomorphism. H&E 200x.

with soft-tissue density and inhomogeneous enhancement. No hepatic mass was seen on CT.

The following laboratory results were obtained: sodium of 142.8 meq/l, potassium of 4.24 meq/l, fasting glucose of 123 mg/dl, resting plasma aldosterone concentration of 78.2 pg/ml, plasma renin activity of 1.2 ng/ml/h, cortisol of 16.58 μg/dL at 8 a.m. and 8.61 μg/dL at 4 p.m., and 24-h urine VMA of 3.9 mg/day (normal, 1.0~7.5 mg/day).

During a right-side laparoscopic adrenalectomy, the BP and HR increased sharply when the tumor was being handled. The BP once rose to 205/115 mmHg, and the HR reached 115/min. Hydralazine was given as needed to control the BP (Fig. 5). After surgery, his BP and HR returned to normal the next

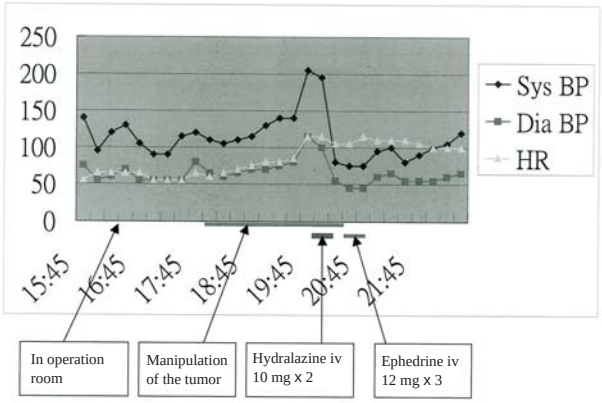

Fig. 5 Vital sign changes during operation in case 1

day. No apparent complications were noted. Pathology confirmed a benign pheochromocytoma (Fig. 6).

Case 4

A 40-year-old woman was undergoing regular follow-up for a hepatic hemangioma in the past 2 years. An adrenal mass was incidentally visualized by abdominal US on her latest visit. The US revealed an estimated 5 x 4-cm nodular lesion with central cystic changes in the suprarenal area, and a right adrenal tumor was suspected. Her past history illustrated no hypertension, Cushingoid appearance, palpitations, headaches, or tremors. At the OPD, her BP was 124/80 mmHg and HR was 80/min. Abdominal CT and MRI delineated a right-side 5 x 5-cm adrenal tumor with central necrosis and soft-tissue density.

The following laboratory were obtained: sodium of 141.8 meq/l, potassium of 4.38 meq/l, fasting glucose of 92 mg/dl, resting plasma aldosterone concentration of 190 pg/ml, plasma renin activity of 1.1 ng/ml/h, cortisol of 14.61 μg/dl at 8 a.m. and 6.52 μg/dl at 4 p.m., 24-h urine metanephrine of 127.6 μg/day, normetanephrine of 1072.2 μg/day, and 3-methoxytyramine of 115.44 μg/day.

During the right-side laparoscopic adrenalectomy, her BP once rose to 220/120 mmHg and HR to 100/min. Nitroprusside was offered for nearly 1.5 h (Fig. 7). After surgery, her BP and HR returned to normal the next day. No apparent complications appeared. Pathology confirmed a benign pheochromocytoma.

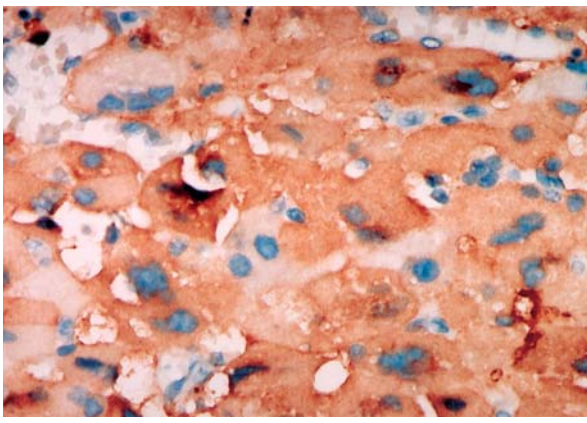

Fig. 6 Synaptophysin staining of the tumor section in case 3.The tumor cells show postivie staining of synaptophysin, a pan-neuroendocrine marker, which is characteristic for medullary cells in the arenal gland. 400x.

DISCUSSION

Most adrenal tumors found incidentally are nonfunctional, but a few of them may be biochemically active. These tumors, including completely silent pheochromocytomas, are rarely reported.[7] For a patient presenting with an adrenal incidentaloma, evidence supports screening for cortisol-secreting adenomas, pheochromocytomas, and primary aldosteronism.[4,5]

A clinical diagnosis of a pheochromocytoma is based on a subjective evaluation of signs and symp-

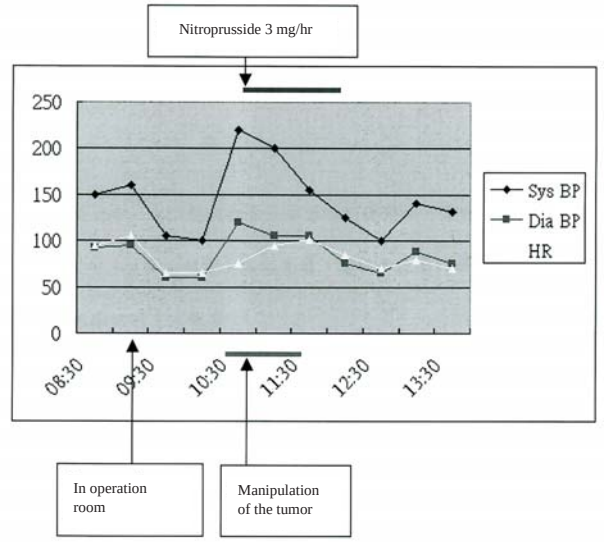

Fig. 7 Vital sign changes during operation in case 1

toms. When one encounters a patient with an incidentally discovered, possible pheochromocytoma, one should initially carefully note the history and perform a physical examination. Of our patients, none had typical symptoms associated with the disease, consisting of hypertension, headaches, palpitations, and sweating attacks. The reasons that such patients have normotension despite high circulating levels of catecholamines were reported to include hypovolemia and nonresponsiveness due to prolonged stimulation.[8] In addition, multiple biochemical tests, including plasma and 24-h urinary catecholamine determinations, must be performed. Typically, a measurement of urinary catecholamines or metabolites that is 2~3 times above the upper normal limit is considered diagnostic of a pheochromocytoma. Incidental tumors tend to exhibit lower 24-h urinary catecholamine values than symptomatic tumors.[9] All symptomatic and most incidental tumors show positive 24-h urinary noradrenaline levels, demonstrating high sensitivity (88.2%).[9] These findings suggest that incidentally discovered pheochromocytomas are functioning despite their lower potential. Among our cases, 2 patients had greater than 200% elevations in urine metanephrine levels. Unfortunately, in the other 2 cases, the biochemical tests were not completed. After biochemical confirmation, imaging studies may help localize the tumor. Pheochromocytomas of the adrenal gland are usually 3~6-cm, rounded masses of soft-tissue density, frequently with central necrosis, and marked enhancement after intravenous contrast material injection. Pheochromocytomas appear hypointense on T1WI and hyperintense on T2WI. Tumors often have a heterogeneous appearance on the latter image due to the presence of cystic regions, necrosis, and fibrosis. With contrast infusion, pheochromocytomas display rapid enhancement. On chemically shifted images, they show a lack of significant signal loss.[3] These characters are similar to adrenal carcinomas except that the margin is irregular and unclear, and the growth is more rapid in malignancies. Of our patients, all had the typical features on imaging studies, and the pheochromocytomas were implied by the imaging results.

If an incidentally discovered tumor proves to be a functioning pheochromocytoma, treatment should theoretically be the same as that for symptomatic disease. Alpha-adrenergic blocking agents have been used preoperatively to control blood pressure to the desired range. Pretreatment with beta-adrenergic blockers is recommended when arrhythmia or tachycardia becomes a problem. The goal of preoperative medical management of a pheochromocytoma for the last 25 years has been to minimize cardiovascular morbidity. The most common approach has been the use of an alpha blockade, such as phenoxybenzamine, which is a long-acting, noncompetitive, alpha-adrenergic blocking agent. The criteria proposed for ensuring adequate preoperative preparation with alpha blockade include supine arterial pressure not to exceed 160/90 mmHg for 48 h, orthostatic hypotension not to exceed 80/45 mmHg, an electrocardiogram free of ST-segment or T-wave changes for at least 2 weeks, and no more than 1 premature ventricular contraction every 5 min.[10] Phenoxybenzamine is initiated at doses of 10 mg every 6 to 12 h and then increased to 30 to 40 mg every 6 h until an optimal dosage is obtained. Side effects, such as orthostatic hypotension, tachycardia, dizziness, and syncope, warrant dose titration. The length of the preoperative therapy remains controversial as several studies have noted conflicting results.[11] Alpha blockade with phenoxybenzamine has several disadvantages. The prolonged action of phenoxybenzamine can intensify hypotension following tumor removal.[12]

Although the preoperative preparations have been well documented for patients with symptomatic pheochromocytomas, they nonetheless remain controversial in patients with no symptoms or signs, i.e., those with clinically silent tumors. What should be done if a patient is normotensive and reveals no sign of dehydration, such as tachycardia, dry mucosa, orthostatic hypotension, or decreased urine output? Do they need to undergo a more-intensive survey and more-invasive investigations, such as central verous pressure to monitor the fluid status before the operation? How should a clinically silent pheochromocytoma be evaluated and what preparation is adequate for such patients? All these questions remain to be answered. Of our patients, the levels of BP were within a normal range, and no apparent evidence of dehydration or hypovolemia was noted before the operation. However, the BP began to rise after entering the operating room and sharply rose inciting a hypertensive crisis in 3 patients. These changes infer that clinically silent pheochromocytomas, even though exhibiting normal blood pressure under usual

conditions, may precipitate a hypertensive crisis in response to stress. Furthermore, 2 cases suffered from sudden hypotension after tumor excision. Intravenous fluid expansion and ephedrine were used to maintain the BP. Thus, clinically silent pheochromocytomas might not be biologically silent, and there may be risks of surgical complications, including hypertensive or hypotensive crises. These changes had no correlation with the size of the tumor in the present patients. Patients with a pheochromocytoma, regardless of whether it is clinically silent, should theoretically be treated the same as those with symptomatic disease.

Intraoperative management of these cases also raises several concerns. Central venous pressure and arterial pressure should routinely be monitored to evaluate the hemodynamic parameters and cardiac function. Enflurane or isoflurane should be used for anesthesia because both decrease myocardial irritability.[13] Intraoperative hypertension should be treated with phentolamine or nitroprusside, and esmolol is excellent for the treatment of intraoperative supraventricular tachycardia, while patients with ventricular arrhythmias usually receive lidocaine. However, the use and regimens of these pharmacological agents vary with different institutions. For persistent hypotension following tumor removal, volume replacement is required in conjunction with careful cardiovascular monitoring.

In conclusion, adrenal pheochromocytomas may be clinically silent but might not be biologically silent at all. Surgical resection of such tumors is indicated, but risks of complications, such as hypertensive or hypotensive crises during the manipulation of these tumors, may occur as with typical pheochromocytomas. Therefore, patients with a pheochromocytoma, even though clinically silent, should be treated the same as those with symptomatic disease. A well-integrated team approach with experienced endocrinologists, surgeons, and anesthesia care is essential for good patient outcomes.

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無症狀嗜鉻細胞瘤併發手術中高血壓危象：四病例分析

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隨著影像技術的進步，意外發現的腎上腺腫瘤日趨增加。據評估，接受腹部電腦斷層掃描的病患中，至少2-3 %可能出現腎上腺偶見瘤，嗜鉻細胞瘤約佔5-23 %。回顧文獻，少有針對無症狀嗜鉻細胞瘤的研究或報告。因此吾人分析4例意外發現的嗜鉻細胞瘤：(1) 沒有嗜鉻細胞瘤的典型症狀；(2) 由生化檢驗，病理檢查和特殊染色確定診斷；(3) 都是良性腫瘤；(4) 手術時，四個患者都出現明顯的血壓變化。甚者，有3名在手術中發生高血壓危象，一度必須使用降血壓藥來控制血壓。兩名患者在切除腫瘤後出現明顯的低血壓，須靠大量靜脈輸液和ephedrine注射以維持血壓。這些變化和腫瘤大小並無相關。雖然這些偶見的嗜鉻細胞瘤臨床上並無表現症狀，但這不表示他們是無分泌功能的。手術切除這些腫瘤是必要的，但是出現併發症的風險，例如高血壓或低血壓危象，並不亞於典型的嗜鉻細胞瘤。因此，此類腫瘤需格外小心處理。(長庚醫誌 2005;28:44-50)

關鍵字：腎上腺瘤，偶見瘤，嗜鉻細胞瘤，高血壓危象。

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