Clinically Silent Pheochromocytoma in Adrenal Incidentaloma：A Case Report and Review of the Literature

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Abstract

Improvements in imaging studies have resulted in an increase in incidentally discovered adrenal tumors. The adrenal incidentaloma was found in at least 2% on abdominal CT imaging, and pheochromocytoma was reported to be about 5.1 to 6.5% among these patients. Here we report a case of silent pheochromocytoma presented as an incidentally discovered adrenal mass on abdominal sonogram. Clinically no apparent symptom and sign of pheochromocytoma was noted. Urine normetanephrine was 1072.2μg/day, 2.4 fold above the upper reference limits, metanephrine and 3-methoxytyramine were still within normal range. Surgical excision of the tumor in the right adrenal gland was performed with pathological report as a benign pheochromocytoma. Although transient hypertension was noted during the procedure of laparoscopic adrenalectomy, there was no complication occurred through the course. Majority of incidentally discovered adrenal masses are nonhypersecretory benign adenomas; but a hormone screening evaluation is necessary to reveal cases with clinically unsuspected hypersecretory nature. For prevention of possible lethal outcome, patients with silent pheochromocytoma scheduled to undergo surgery should be treated according to the hemodynamic parameters. (J Intern Med Taiwan 2003;14:248-254)

Key Words：Incidentaloma, Pheochromocytoma, Adrenal tumor

Introduction

As the advances in imaging diagnosis of high-resolution ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI), a more frequency of incidentally discovered adrenal tumors were reported, including pheochromocytoma1,2. Due to the limited image of US, CT has been used to confirm the adrenal masses and it is reported to identified adrenal masses as small as 0.5 cm or small in diameter 3. The prevalence of adrenal masses are found in at least 2% on CT

scanning for reasons other than suspected adrenal pathology 4,5. Among patients with adrenal incidentalomas, approximately 5.1% 5 to 6.5% 4, even up to 23% 2, proved to have pheochromocytomas. And 10% of adrenal pheochromocytomas have presented as adrenal incidentalomas, even with clinically silent 5.

Pheochromocytomas are rare tumors found in less than 1% of the populations with hypertension. Although the majority of patients are symptomatic, 10-30% of pheochromocytomas are clinically silent 6. Identification of the hormone activity and malignant potential among patients with adrenal incidentalomas are clinically important. Failure to recognize and treat a pheochromocytoma could prove a fatal oversight. Here we report a case of incidentally discovered, clinically silent and pathologically proved benign pheochromocytoma. The management of this silent pheochromocytoma and its atypical presentation are discussed.

Case Report

A 39-year-old woman, previously healthy, received regular follow-up for the hepatic hemangioma in recent 2 years. She presented to endocrine OPD for an incidentally discovered adrenal mass found by abdominal US this time. The US revealed a round isoechoic nodular lesion measured about 5×4cm in size with central cystic changes at the suprarenal area, and right adrenal tumor was suspected. Review her past history, no hypertension, no Cushingoid appearance, no edema, no apparent body weight change, no much hair loss or hirsutism, no purple striae on abdomen or limbs were noted, except occasional palpitation noted on severe angry. At OPD, blood pressure （BP） was 125/75 mmHg, heart rate （HR） was 80/min, and respiratory rate （RR） was 18/min. Thyroid hormone tests revealed euthyroid status. Abdominal CT was preformed and identified an adrenal tumor, right side, 5×5 cm, with central necrosis and soft-tissue density (Fig 1) . Pheochromocytoma was highly impressed. On the other hand, a series of biochemical tests and hormone study was performed. Laboratory data revealed RBC: 3.45×10 6 /μL, Hb: 9.4 g/dL, Hct: 28%, WBC: 9500/μL, BUN: 7.5 mg/dL, creatinine: 0.81 mg/dL, blood sugar (AC) : 92 mg/dL, sodium: 141 mg/dL, potassium: 4.38 mg/dL, calcium: 8.0 mg/dL, resting plasma aldosterone concentration 190 pg/mL (normal 30 to 160 pg/mL) , plasma renin activity 1.1 ng/mL/hour (normal 0.15 to 2.33) , cortisol level at 8 am : 14.61μg /dL (normal 6 to 23) , 4pm: 6.52μg/dL (normal 3 to 14) ; 24-hour-urine metanephrine 127.6μg/day (normal 52 to 341) , normetanephrine 1072.2μg /day (normal 88 to 444) , 3-methoxytyramine 115.44μg/day (normal 10 to 296) . MRI was arranged for study of phenotype and chemical shift, and revealed an adrenal tumor about 4 cm in diameter, right side (Fig 2) . The lesion revealed intermediate signal intensity in T1WI and heterogenously high signal intensity in T2WI. Central necrosis and

prolonged enhancement of the tumor was noted. No direct invasion, lymph node involvement or distant metastasis was found. These imaging findings highly suggest the pheochromocytoma.

Under the impression of silent pheochromocytoma in adrenal incidentaloma, she received operation with laparoscopic adrenalectomy, right side. Before entering the operation room, the BP once elevated to 150/96 and HR elevated to 95/min, but the patient denied any discomfort. On the course of operation, the BP once elevated to 220/120 mmHg and HR came to 100/min, and nitroprusside was given with for about 1.5 hours introperatively (Fig 3). After completion of surgery, her BP and HR turned to normal range through next day. No apparent complication was noted.

Gross pathology demonstrated a large tumor, 5.0×3.0×2.5 cm, 31gm, right adrenal gland. The tumor configuration is well-demarcated, brownish hard cut surface. Microscopic examination revealed tumor cells arranged in anastomosing trabecular pattern and interrupted by thickened fibrous septa with massive hemorrhage. The tumor cells are polygonal with finely granular and eosinophilic cytoplasm (Fig 4). A focus of capsular invasion was noted while there is no further evidence of malignancy (Fig 5) and a Pheochromocytoma of the Adrenal Gland Scaled Score was used (PASS <4), to confirm its benign fashion 7.

Besides, for screening of the possibility of multiple endocrine neoplasia (MEN syndrome) type II. Serum level of calcium and thyroid sonography was performed which showed normal serum calcium level and no evidence of thyroid nodule or hyperplasia. There was no family history of pheochromocytoma or MEN type II. Two days after operation, she was discharged smoothly.

Discussion

Pheochromocytomas are catecholamine-producing tumors of neuroectodermal origin identified by the presence of cells with positive chromaffin stain. The tumor may occur in patients of any age with equal frequency in both sexes. In general, 10% of these tumors are extra-adrenal, 10% are malignant, 5% occur bilaterally, and 10 % are inherited as an autosomal dominant pattern 8, 9.

The diagnosis of pheochromocytoma is usually suggested by its clinical symptoms. Hypertension is the most common clinical manifestation of pheochromocytoma and is present in 90-100% of patients. Sustained hypertension is seen in half, paroxysmal hypertension in a third, and normal blood pressure in less than a fifth of patients10. The classical triad consisted of headache, palpitation and diaphoresis. These episodes may occur daily or monthly. More than 90% of patients presented with, at least, two of the three symptoms in the classic triad 10. Less common symptoms include tremor, angina, nausea, Raynaud 掇 phenomenon, livedo reticularis, and mass effect from the

tumor.

Completely silent pheochromocytomas are reported rare 9-11. In our case, she is asymptomatic and normotensive except occasional palpitation noted on severe angry which is rather unspecific.

Therefore, even when clinically silent, patient with an incidentally discovered adrenal mass, should be carefully screen for the possibility of functional activity as pheochromocytoma, the diagnosis is made with the demonstration of elevated circulation or urinary catecholamines or metabolites. Typically, a measurement of urinary catecholamines or metabolites that is two or three times above the upper limit of normal is considered diagnostic of pheochromocytoma 11.

Because of the dramatic symptoms, functional tumors are usually small when detected, whereas nonfunctional tumors may be large 12. For pheochromocytomas, the mean diameter of incidental tumors was also significantly larger than that of symptomatic tumors 13, 14. Crout and Sjoerdsm found that pheochromocytomas 50gm. or larger are often asymptomatic because secreted catecholamines are metabolized within the tumor 13. In contrast, tumors small than 50 gm. have slow turnover rates and release free catecholamines into the circulation, exhibiting persistent symptoms and signs15. As in our case, her adrenal tumor is large in size, though weight is less than 50gm., and clinically silent. The reasons for finding these normotensive patients despite high circulating level of catecholamines are reported to include relatively hypovolemia and poor responsiveness due to prolong stimulation14.

The imaging phenotypes of adrenal tumors (Table 1) may help us to distinguish the pheochromocytoma from other tumors 5. The size and appearance of an adrenal mass on CT or MRI may help distinguish between benign and malignant tumors. Particularly, MRI can better delineate the tissue character and extent of the neoplasm. Further more, I131 metaiodobenzyl guanidine (MIBG) can be useful in determining the functional character of a tumor and locating occult secondary or metastatic lesion 15. In our case, the US revealed a round isoechoic nodular lesion measured about 5×4cm2 in size with central cystic changes at the suprarenal area, and right adrenal tumor was suspected. The Abdominal CT identified a solitary adrenal tumor, right side, 5×5 cm2, with central necrosis, soft-tissue density, clear margins and no calcifications. Contrast media enhancement usually revealed vascular, marked enhancement. The CT attenuation value, conventionally expressed in Houns-field units (HU) , >10 HU without contrast and > 40 HU at 30 minutes after contrast administration. The MRI imaging reveals markedly hyperintense on T2-weighted image. These imaging feature all characterized the pheochromocytoma.

In our case, to determine whether the patient with adrenal incidentaloma has subtle evidence of presence of functional tumor such as Conn’s disease, Cushing’s syndrome,

pheochromocytoma or virilizing or feminizing tumors, serum level of aldosterone concentration and plasma renin activity, serum cortisol level with diurnal rhythm, and urine level of metanephrines were checked. Combining the history, physical finding, and the biochemical study, the possible diagnoses of Conn's syndrome, subclinical Cushing's syndrome or virilizing or feminizing tumors were initially excluded. Confirmatory biochemical tests to document increased levels of catecholamines are necessary to make the diagnosis of pheochromocytoma. The sensitivity and specificity of 24-hour urine catecholamines for the diagnosis of pheochromocytoma are 86 and 88%, respectively, urinary metanephrines are 77% and 93%, urinary vanillylmandelic acid are 64% and 95% respectively 17. Recently, plasma free metanephrine is reported to have higher sensitivity (99%) and good specificity (89%) , and is recommended as the test of choice for excluding or confirming the diagnosis of pheochromocytoma 17,18, however, this test is not currently available in our institute.

CT-guided fine-needle aspiration (FNA) may be helpful in the diagnostic evaluation of patients with a history of cancer and a heterogeneous adrenal mass with a high attenuation value (> 20 HU) 18. However, pheochromocytoma must be excluded before FNA of an adrenal mass is attempted in order to avoid the potential for hypertensive crisis 13, 18.

As the treatment of incidentally discovered adrenal tumor, the therapeutic plan focus on whether the lesion is biochemically active (functional) and benign or malignant. Patients with pheochromocytoma, even when clinically silent, are at risk for a hypertensive crisis and should treat theoretically the same as that for symptomatic disease. Phenoxyben-zamine, an alpha-adrenergic blocking agent with beta-adrenergic blockers when arrhythmia or tachycardia should be used accordingly and schedule for undergo adrenalectomy 13,18. Intraoperative hypertension, due to sudden release of catecholamines caused by surgical stress or procedure, should be treated with phentolamine or nitroprusside, propanolol for intraoperative supraventricular tachycardia, lidocaine for ventricular arrhythmias and close evaluation of the hemodynamic parameters and cardiac function are necessary perioperationally13. For persistent hypotension following tumor removal, volume replacement is required in conjunction with careful cardiovascular monitoring13.

Conclusion

As the improvement and more frequent use of imaging study, the incidentally discovered pheochromocytoma may not be a rare finding as we previously thought. Although majority of adrenal incidentalomas are nonhypersecretory benign adenomas; a substantial percentage among these incidentalomas are hormonally active tumor and

less frequently, adrenocortical carcinoma, which early diagnosis and treatment is critica l5,19-20. Hormone screening evaluation is necessary to reveal cases with clinically unsuspected hypersecretory nature. For prevention of possible lethal outcome, patients with silent pheochromocytoma scheduled for surgery should be closely evaluated and treated according to the hemodynamic parameters and cardiac function.

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Table 1. Imagine Phenotypes of Pheochromocytoma (adapted from Reference 5)

Size-- large, typically >3cm
Shape-- round to oval with clear margins
Texture-- heterogeneous with cystic areas
Laterality-- usually solitary and unilateral
Contrast media enhancement-- usually vascular, marked enhancement
CT-->10 HU without contrast and > 40 HU at 30 minutes after contrast administration
MR imaging-- markedly hyperintense compared with liver on T2-weighted image
Hemorrhage and cystic necrotic areas common; calcifications is uncommon
Growth-- usually slow.

Fig.1. Abdominal CT with contrast enhancement reveal an adrenal tumor, right side, 5×5 cm2, with central necrosis and soft-tissue density. The tumor is vascular, marked enhancement. No obvious calcification are seen within this mass.

Fig.2. Coronary section of MRI imaging also revealed an adrenal tumor with contrast enhancement, about 5 cm in length, in right adrenal gland.

Fig.3. Vital signs change during operation

Fig.4. The tumor cells are polygonal with finely granular and eosinophilic cytoplasm. Nest of large uniform cells with rounded nucleoli arranged in Zellballen pattern was 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 200×.

Fig.5. A focus of capsular invasion was noted while there is no further evidence of malignancy. Pheochromocytoma of the Adrenal Gland Scaled Score（PASS）<4 favor a benign fashing in clinical practice 7. H&Ｅ 40×.

腎上腺偶見瘤中的無症狀嗜鉻細胞瘤：病例報告暨文獻回顧

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摘　　要

由於影像學診斷技術的進步，經由腹部影像而意外發現的腎上腺腫瘤逐日增加。據統計，腹部電腦斷層發現這些腎上腺偶見瘤的機率約是 2 %，其中嗜鉻細胞瘤約佔 5.1 至 6.5%。本文報導一個案例，經由腹部超音波檢查意外發現一腎上腺腫瘤。臨床上病人並無任何相關徵狀，但其尿液中正腎上腺素代謝物的濃度卻是正常值上限的 2.4 倍，腎上腺素代謝物則是在正常範圍。病人接受手術切除腫瘤，病理檢查證實是良性嗜鉻細胞瘤。雖然術中血壓一度竄升，但經由適當藥物控制，病人並無出現任何併發症。雖然意外發現的腎上腺腫瘤大多是無功能之良性腺瘤，但對腎上腺偶見瘤進行適當的功能檢測是必要的，以期篩選出無症狀之功能性腫瘤而給予適當的治療。爲避免可能的併發症，手術治療無症狀嗜鉻細胞瘤的患者，應根據其血行生理狀態而做適當的處置。