Adrenal Incidentalomas in Taiwan: High Prevalence and Malignancy Rate

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Background: The endocrine adrenal gland has 3 zones comprised of the cortex and medulla. The character of multi-hormonal expression results in multiple clinical manifestations. To define the clinical characteristics of adrenal tumors in Taiwan, we reviewed 336 pathologically proven adrenal tumors at Chang Gung Memorial Hospital in Linkou.

Methods: We retrospectively analyzed 258 pathologically proven adrenal tumors with sufficient data treated from 1983 to 2000. Among them, 174 (67%) were functional and 84 (33%) were nonfunctional. The diagnosis was based on clinical features, hormonal status, imaging studies, and pathology.

Results: Of the 258 patients, 161 were women (mean age, 38.5¡ 15.4; range, 1-75 years) and 97 men (mean age, 41.6¡ 17.8; range, 1-81 years). The prevalence of cortical tumors was much higher in females than in males. Fifty-two percent of patients with an adrenal tumor were diagnosed at an age between 30 and 50 years. Incidentalomas (N=84) accounted for about 1/3 of total tumor cases. Of the 46 cases proven to be malignant, 40 (87%) were found incidentally. All malignant tumors had a diameter of greater than 3 cm. Postoperative adrenal insufficiency was present in 18% of cases, and overall mortality in this study was 0.4%.

Conclusions: In our series, adrenal incidentalomas corresponded to about 1/3 of adrenal tumors and accounted for 87% of malignancies. It is mandatory to increase medical attention for incidentally found adrenal masses in Taiwan. Those incidentalomas with a diameter of more than 3 cm should undergo a pathological examination.

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Key words: adrenal incidentaloma, Cushing's syndrome, primary aldosteronism, adrenal malignancy.

The clinical presentations of adrenal tumors are usually highly variable due to characteristics of the endocrine adrenal gland. Tumors of the adrenal cortex, whether benign or malignant, are often associated with an excess production of steroids, whereas tumors of the medulla are associated with overproduction of catecholamines. The malignancy rates of adrenal tumors, however, were low in previous reports.[1,2] With recent advances in imaging techniques, many asymptomatic adrenal incidentalomas

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are now being discovered.[3-7] The malignancy rate of adrenal incidentalomas is usually higher than that of symptomatic tumors.[3-8] Surgical approaches are still the mainstay of treatment for functional and primary malignant adrenal tumors, both for curing and palliation, with low morbidities and mortalities. For this report, we reviewed a series of 336 adrenal tumors at Chang Gung Memorial Hospital in Linkou, northwestern Taiwan and found a predisposition for malignant incidentalomas.

METHODS

In total, 336 patients with adrenal tumors were traced from 1983 to 2000 at Chang Gung Memorial Hospital, including 78 cases with missing records or data. Therefore, we used the remaining 258 cases for this series. Among them, 161 cases were women (mean age, 38.5¡ 15.4; range, 1-75 years) and 97 were men (mean age, 41.6¡ 17.8; range, 1-81 years). The patients had undergone clinical, hormonal, or imaging evaluation. Localization of the adrenal tumor was based on imaging techniques including ultrasonography (US), computed tomography (CT), and/or magnetic resonance imaging (MRI) or adrenal scintigraphy including I-6-β-iodomethyl-19-norcholesterol (NP-59) for cortical tumors[9] and metaiodobenzylguanidine (MIBG) for medullary tumors.[10]

Hormone studies included serum cortisol and adrenocorticotropic hormone (ACTH), plasma aldosterone and rennin, and/or serum dehydroepiandrosterone. Twenty-four-hour urine was collected for free cortisol, vanillylmandelic acid (VMA), or catecholamine examinations according to the clinical features. Dynamic tests such as dexamethasone suppression test or saline loading test were performed for clinical confirmation. Most cases received clinical, hormonal, and imaging evaluations in the medical department. Assays of hormones were performed by radioimmunoassay, while VMA and catecholamine were quantified by enzyme-linked-immunosorbent assay.

Functional adrenal tumors were defined as tumors with elevated hormone levels regardless of symptoms; otherwise, tumors were defined as nonfunctional. Regardless of the hormonal status, a tumor was defined as an incidentaloma when a mass was detected by imaging studies in an otherwise asymptomatic patient. Most of those masses were discovered incidentally by physical examination, US, or CT during routine health examinations. The statistical analysis of tumor size between benign and malignant adrenal incidentalomas used the Chi-squared test. Overall, 251 patients underwent surgical removal of the tumor. Among them, 102 patients underwent a midline abdominal approach, 97 patients underwent a unilateral subcostal approach, 1 underwent a bilateral subcostal approach, 18 patients underwent a flank approach, 13 patients underwent an 11th rib approach, and 20 patients underwent a 12th rib approach. The other 7 patients with metastatic tumors received a biopsy only.

RESULTS

The clinical features of the 258 patients with adrenal tumors are summarized in Table 1. The ratio of symptomatic tumors to incidentalomas was 2 to 1 (174 vs. 84 cases). All symptomatic tumors were functional. Among them, 52 cases consisted of Cushing's syndrome, 68 tumors produced autonomous aldosterone secretions, and 53 tumors originated from the adrenal medulla and produced excess catecholamine secretions (i.e., pheochromocytomas). The 24-hour urine VMA levels ranged from 7.0 to 161.9 mg/day. An 8-year-old girl with precocious puberty and premature breast development was diagnosed with adrenogenital syndrome.

Table 1. Comparison of Tumor Characteristics between Symptomatic Adrenal Tumors and Incidentalomas

	Symptomatic tumors				Incidentalomas		Total
	Functional				Silent	Non-functional	
	Cus	PAL	PHE	ADS	PHE		
Total no.	52	68	53	1	17	67	258
Male	7	19	28	0	7	36	97
Female	45	49	25	1	10	31	161
Left	33	37	23	0	8	29	129
Right	18	30	29	1	9	38	125
Bilateral	1	1	1	0	0	0	3
Benign	51	68	48	1	15	29	212
Malignant	1	0	5	0	2	38	46

Abbreviations: Cus: Cushing's syndrome; PAL: primary aldosteronism; PHE: pheochromocytoma; ADS: adrenogenital syndrome.

The incidence of adrenocortical tumors was higher in females than in males. Cushing's syndrome was 6.4 times and primary aldosteronism was 2.6 times more frequent in females than in males. However, tumors arising from the medulla (pheochromocytomas) showed no gender difference. Most (80%) of the adrenal incidentalomas were nonfunctional, and only 20% were silent pheochromocytomas. Patients with silent pheochromocytomas had no prominent clinical manifestations, and their 24-hour urine VMA levels (4.5 to 124.5 mg/day) were comparable to those with functional pheochromocytomas.

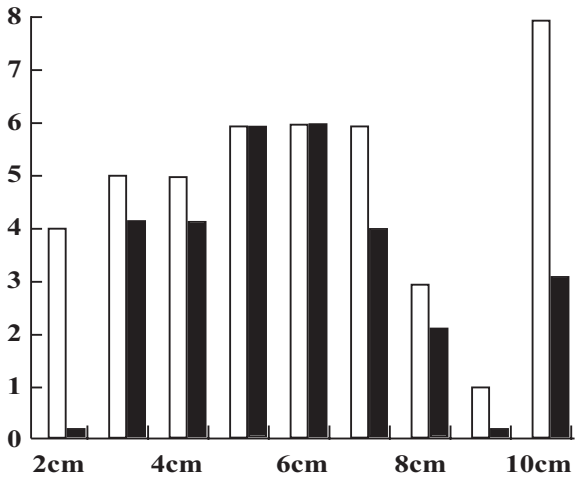

Fig. 1 Tumor size of 73 primary adrenal incidentalomas. All primary adrenal malignant incidentalomas had a diameter of greater than 3 cm as shown, but no significant difference in size between benign and malignant tumors was seen ($p = 0.934$).

Fifty-two percent of patients with adrenal tumors were diagnosed at the age of between 30 and 50 years. There was no significant difference between tumors developing on the right or left side, and only 3 (1.1%) patients had bilateral tumors. In this study, adrenocortical adenomas accounted for 52% of cases, and it was the most common neoplasm.

Table 2 shows the pathological characteristics of symptomatic tumors and incidentalomas. There were 5 cases of malignancy in symptomatic tumors,

Table 2. Pathological Characteristics of Symptomatic Adrenal Tumors and Incidentalomas

	Pathology	Number
Symptomatic tumors	**Benign tumors**	**168**
	Adrenocortical adenoma	120
	Pheochromocytoma	48
	Malignant tumors	**6**
	Adrenocortical carcinoma	1
	Pheochromocytoma	5
	Total	**174**
Incidentalomas	**Benign tumors**	**44**
	Adrenocortical adenoma	16
	Myelilipoma	8
	Ganglioneuroma	5
	Pheochromocytoma	15
	Malignant tumors	**40**
	Adrenocortical carcinoma	5
	Pheochromocytoma	2
	Ganglioneuroblastoma	4
	Neuroblastoma	16
	Metastatic carcinoma	11
	Undiagnosed tumor	2
	Total	**84**

Table 3. Characteristics of 11 Metastatic Tumors of the Adrenal Gland

Case	Age (yr)	Gender	Pathology	Primary site	Tumor diameter (cm)	Side
1	44	female	adenocarcinoma	ovary	10	right
2	44	male	HCC	liver	Bx	left
3	65	male	HCC	liver	Bx	left
4	65	male	HCC	liver	10	right
5	75	female	adenocarcinoma	lung	Bx	left
6	69	male	adenocarcinoma	lung	12	left
7	72	male	adenocarcinoma	lung	5	left
8	54	male	squamous cell carcinoma	lung	8	left
9	44	male	malignant carcinoid tumor	kidney	3	left
10	42	female	TCC	kidney	2	left
11	70	female	TCC	kidney	7	right

Abbreviations: HCC: hepatocellular carcinoma; TCC: transitional cell carcinoma; Bx: biopsy.

compared to 40 cases of malignancy found in the incidentalomas. The malignant predisposition of these adrenal incidentalomas was 47.6% (40 out of 84). In a total of 46 cases of pathologically proven adrenal malignancy, 87% cases were incidentally found. Six cases of malignant tumors originated from the adrenal cortex and 7 cases from the medulla. As shown in Fig. 1, there was no significant difference in tumor size between benign and malignant tumors ($p=0.963$). However, all malignant tumors had a diameter of more than 3 cm. There were 20 cases of neuroblastomas and ganglioneuroblastomas, and all were diagnosed before the age of 14 years.

In the 11 cases with metastatic cancer, the primary sites were usually the lung, liver, and kidney with 1 case originating from the ovary (Table 3). Interestingly, 8 of 11 metastatic tumors were found on the left side.

Postoperative complications included 53 patients (including 46 with Cushing's syndrome) with postoperative adrenal insufficiency, 1 patient with acute renal failure, 1 patient with wound infection, and 1 patient with postoperative mortality.

DISCUSSION

Classifying adrenal tumors as functional or nonfunctional, based on their hormone status, is important for their appropriate evaluation and management. Functional adrenal tumors usually present typical symptoms and signs caused by excess hormone(s). Functional tumors of the adrenal cortex present as Cushing's syndrome, primary aldosteronism, or adrenogenital syndrome, while functional medullary tumors present as pheochromocytomas. With progress in imaging techniques and their convenient application, reports of adrenal tumors detected incidentally (incidentalomas) during routine physical examinations or surveys for other diseases, have increased since 1980.[1-5] In our series, 84 patients with incidentalomas accounted for 33% of all cases.

Osella et al.[11] carefully studied 45 patients with incidentally discovered adrenal masses. From their data, Griffing[12] made the following points about such masses: 1) a diagnosis of subclinical or "silent" hypercortisolism (normal concentrations of urinary-free cortisol) should always be considered, and dexamethasone suppression testing may be required; 2) fine-needle aspiration is not useful in differentiating adenomas from carcinomas and should be used only when metastasis is suspected; and 3) "silent" pheochromocytomas may be more common than previously thought, and the diagnosis should be assumed until assiduously ruled out. In our series, incidentalomas accounted for about 1/3 of cases and corresponded to 87% (40/46) of total pathologically proven malignancies. It is mandatory to focus medical attention on the discovery of adrenal incidentalomas in Taiwan.

The biochemical diagnosis of adrenal Cushing's syndrome includes 24-hour urinary free-cortisol, low-dose dexamethasone testing, plasma ACTH, and high-dose dexamethasone testing. An NP-59 adrenal scan with/without CT or MRI is used to confirm the diagnosis.[13-18] In our study, Cushing's syndrome accounted for 20% of adrenal tumors, and the positive rate was 98% (51/52) by high-dose dexamethasone suppression test; the exception was 1 patient who was not tested. In accordance with other studies,[18] female patients and the left adrenal gland were predominantly affected in our series. It is unclear why there is a preference for the left adrenal. The preponderance of affected female patients may be due to the early presenting symptoms of Cushing's syndrome such as hirsutism and oligomenorrhea which uniquely affect women.

Hypertension, hypokalemia, suppressed plasma rennin activity, and increased aldosterone excretion characterize the syndrome of primary aldosteronism first described in 1955. The prevalence of primary aldosteronism ranges from 0.05% to 2% of the population with hypertension and should be considered in patients presenting with neuromuscular weakness associated with hypokalemia, regardless of the degree of hypertension.[19] The adrenogenital syndrome caused by an adrenal cortical tumor has rarely been reported, with only 1 case in the present series.

A pheochromocytoma is a rare tumor arising from the chromaffin tissue and accounts for fewer than 0.3% of all cases of hypertension; it has presenting symptoms of palpitation, headache, sweating, and anxiety. Ronald et al.[20] carefully studied 35 patients with pheochromocytomas and found that the most-sensitive laboratory diagnostic tests were plasma total catecholamines (95%) and urine total metanephrines (100%). Testing for urine VMA, which is less expensive and easier to perform than many other tests, had a slightly lower sensitivity

(89%). In our study, urine VMA was the most widely used method for the diagnosis of pheochromocytomas, with a sensitivity of 84% (59/70). In addition, the finding that 20% of adrenal incidentalomas were pheochromocytomas is in agreement with Osella et al.,[11] suggesting that "silent" pheochromocytomas may be more common than previously thought.

Adrenal insufficiency usually occurs after removal of the adrenal mass, and supplemental therapy with steroids may be required.[17] Postoperative adrenal insufficiency was the most common complication in our series. Most cases (46/53) occurred in patients with Cushing's syndrome. The persistent hypercortisolemia suppresses secretion of ACTH by the pituitary, which causes atrophy of non-tumor adrenal cells.

In an asymptomatic patient with an incidentaloma, the screening should include serum potassium level to exclude an aldosteronoma, urinary levels of VMA and catecholamines to exclude a pheochromocytoma, and a single 1-mg dose of an overnight dexamethasone suppression test for Cushing's syndrome.[21] In addition, an adrenal scan with NP-59 was used to identify adrenal masses. This compound is taken up by functional adrenal tumors, even at a subclinical level, but not by the suppressed contralateral gland.[22]

Surgical removal of adrenal tumors is the only curative approach. Surgery is principally indicated for functional adrenal tumors regardless of their characteristics, malignant tumors regardless of their hormone status, and pheochromocytomas with or without symptoms. The surgical details of an open adrenalectomy have been described previously.[23] Recently, the standard for laparoscopic adrenalectomies was established[24] with enhanced recovery, shorter hospital stay, fewer complications, and greater cost-effectiveness.[25,26] When performed by well-trained and skilled surgeons, the laparoscopic approach is superior to an open adrenalectomy.[24,27]

Medical treatment provides adjuvant or palliative therapy for patients with adrenal tumors. It is also used as a preparation for surgery and as complementary therapy afterwards, or in patients with contraindications for surgery. For patients with functional adrenal tumors, medical treatment may be required for several weeks before tumor resection, e.g., antialdosterone drugs should be used before surgery to correct the hypokalemia in patients with primary aldosteronism and preoperative α-adrenergic blockers, and calcium channel blockers should be used in patients with a pheochromocytoma to reduce blood pressure, increase the intravascular volume, and prevent paroxysmal hypertension before surgery. In patients with a cortisol-producing adenoma, special attention should be paid to perioperative steroid replacement, because removal of the functional tumor may precipitate an adrenal crisis unless supplemental corticosteroids are administered postoperatively.

In conclusion, we found a high prevalence of and a malignant predisposition for incidentalomas in this Taiwanese series. It is mandatory to increase medical attention when an adrenal mass is incidentally found. Those incidentalomas with a diameter of greater than 3 cm should undergo a pathological examination.

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在台灣的腎上腺偶發瘤：高惡性比例及高盛行率

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背 景：腎上腺包含三層皮質及髓質。其具多種荷爾蒙分泌的特性，造成臨床表現的多樣性。爲了研究腎上腺腫瘤在台灣人的表現，因此我們將長庚醫院病理診斷確定的腎上腺腫瘤加以分析。

方 法：我們分析從1983到2000年258位有腎上腺腫瘤且其資料完整的病人，其中174例是功能性而84例是非功能性。其診斷主要是根據臨床表現、賀爾蒙狀況，影像檢查及病理報告。

結 果：258位病人中，包括161位女性 (平均年齡：38.5±15.4歲) 及97位男性 (平均年齡：41.6±17.8歲)。腎上腺皮質腫瘤的盛行率女性比男性高。52%病人診斷年紀在30-50歲之間。在所有腫瘤中，無症狀之偶發瘤佔1/3 (84例)，且46例惡性腫瘤中40例(87%)是偶發瘤。所有惡性腫瘤直徑均大於3公分。術後腎上腺功能不足有18%、死亡率爲0.4%。

結 論：在我們的系列，偶然發現的腎上腺腫瘤約佔腎上腺皮質腫瘤的三分之一，及惡性腫瘤的87%。因此在台灣對腎上腺偶發瘤應提高注意，而直徑大於3公分的偶發瘤則應該接受病理檢查。

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關鍵字：腎上腺偶發瘤，庫欣氏症，原發性多醛酮症，腎上腺惡性腫瘤。

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