

Clinical Characteristics for 348 Patients with Adrenal Incidentaloma

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Background: Adrenal incidentaloma is an adrenal neoplasm frequently encountered in clinical practice for which detection rates have recently increased. We describe here the clinical characteristics of adrenal incidentalomas.

Methods: A retrospective study was performed examining the age, sex, location, size, function, and the histological findings for 348 patients with an adrenal mass discovered incidentally on computed tomography (CT) undertaken for health examination or nonadrenal disease from August 2005 to May 2012.

Results: Patients consisted of 156 males (44.8%) and 192 females (55.2%), aged between 20 and 86. Adrenal masses were most commonly found in patients in their sixth decade (32.5%). Regarding the location of the masses, 62.0% were found in the left adrenal gland, 30.2% were found in the right, and 7.8% were found bilaterally. Of all of the masses analyzed, 87.1% were 1 to 4 cm in size, and an adenoma-like appearance was the most common finding (75.3%) seen on CT scans. Hormonal analysis showed that 82.2% of the masses were nonfunctioning, 6.0% were diagnosed as subclinical Cushing's syndrome, 4.6% were aldosterone-producing adenomas, and 7.2% were pheochromocytomas. Adrenalectomy was performed in a total of 69 patients having adenoma (50.7%), pheochromocytoma (24.6%), and carcinoma (4.3%).

Conclusion: The characteristics of benign, malignant, nonfunctional, and functional adrenal masses that were incidentally found at our hospital were similar to those presented in other studies.

Keywords: Adrenal incidentaloma; Cushing syndrome; Pheochromocytoma

INTRODUCTION

As the frequency of abdominal computed tomography (CT) scanning increases, for various reasons, the detection rate for adrenal incidentalomas has also risen [1]. Adrenal incidentalomas are adrenal masses that are discovered incidentally during imaging procedures performed for clinical symptoms unrelated to adrenal disease. Along with recent advancements in imaging technology, detection of adrenal incidentalomas has remarkably increased [2,3].

Although most adrenal incidentalomas are benign, nonfunctional tumors, 10% of these masses are related to abnormal hormone secretion [4], though they are rarely found to be malignant [5]. Thus, it is very important to distinguish whether a mass is functional, nonfunctional, or possibly malignant. Various imaging techniques and biochemical tests are utilized to formulate the differential diagnosis for an adrenal incidentaloma [6], of which the most frequently used method is nonenhanced CT [7,8]. Presence of intracytoplasmic lipid on CT is a critical feature that differentiates between benign and ma-

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lignant adrenal tumors [9]. A high level of intracytoplasmic lipid with a low Hounsfield unit (HU) measurement is observed in adrenal adenomas, which accounts for the majority of adrenal incidentalomas [10]. A reading of less than 10 HU on nonenhanced CT indicates an adrenal tumor within intracytoplasmic lipid content, and can be diagnosed as an adenoma with 71% sensitivity and 98% specificity [11]. Enhanced washout measurements on enhanced CT or chemical shifts with magnetic resonance imaging examination are also useful in creating a differential diagnosis [12]. Benign masses exhibit a fast enhanced washout, while the washout is delayed if the mass is malignant. If enhanced washout is greater than 50% at 10 minutes after injection of a contrast medium, the mass can be diagnosed as benign with 100% sensitivity and specificity [12,13].

Many studies have been done in other countries regarding the characteristics of adrenal incidentalomas. Based upon those studies, recommendations have been made on diagnosis and treatment. However, studies on the Korean population have been insufficient, with only a couple of case reports published previously. As in other countries, the incidence of accidentally detected adrenal masses has increased in Korea, and large-scale studies are needed to establish relevant statistics and characteristics of these masses. Accordingly, the objectives of this study were to investigate the clinical characteristics in 348 patients with adrenal incidentaloma found on CT and to compare the results with studies conducted previously in other countries as well as prior studies done in Korea.

METHODS

The study was carried out in a total of 348 subjects who had adrenal masses discovered on CT that was indicated for non-adrenal concerns, such as health examination, following up lung nodules seen on chest X-ray, possible cholecystitis, abdominal hernias, and in consideration of other abdominal or urinary tract symptoms. Patients were collected from August 2005 to May 2012 and none exhibited clinical symptoms of adrenal disease. A retrospective study was conducted, and data was gathered on age, sex, anatomic characteristics such as size and location of the mass, endocrine function of the mass, as well as histological findings. Age, sex, and medical history were culled from patient medical records, while the location, size, and shape of the masses were based on findings from imaging examinations. In addition, HU, which are useful in differentiating between benign and malignant masses on non-

enhanced CT images, were measured. Regarding functionality, hormone tests relating to pheochromocytoma, subclinical Cushing's syndrome, and aldosterone secreting adenoma, which were the most frequently diagnosed conditions of the clinically significant functional adrenal masses, were carried out. The same screening tests were applied throughout all patients: with pheochromocytoma, a 24-hour urinary vanillyl mandelic acid (VMA), total metanephrine, and three fractions of plasma catecholamine (epinephrine, norepinephrine, and dopamine) were determined; for subclinical Cushing's syndrome, a 24-hour urinary free cortisol was measured; for aldosterone secreting adenoma, a plasma aldosterone, renin activity, and the potassium level were measured. If the 24-hour urinary VMA and total metanephrine were higher than the reference values, the mass was diagnosed as a pheochromocytoma; if the 24-hour urinary free cortisol was higher than that of the reference value, and the patient lacked any specific symptoms of Cushing's syndrome, it was diagnosed as subclinical Cushing's syndrome; when plasma aldosterone was higher and plasma renin activity lower than their respective reference values, and the ratio of plasma aldosterone to renin activity was greater than 20 with hypokalemia present, diagnosis of aldosterone secreting adenoma was made. A physiological saline load test was performed as a confirmatory test in only one patient of 13 patients diagnosed with aldosterone secreting adenoma during the screening. If the diagnosis criteria were met for any of the three aforementioned conditions, it was classified as a functional tumor.

Determination of malignancy was based upon histological findings of surgically resected specimens. Of the patients with functional tumors, malignant characteristics were discovered in eight out of 25 patients with pheochromocytoma, 16 out of 21 with subclinical Cushing's syndrome, three out of 16 with aldosterone secreting adenoma patients. Five of nine patients who had findings concerning for malignancy on CT did not receive surgery in our hospital. In those cases, either follow-up was not performed in our hospital or surgery was performed at an outside hospital. Of the patients diagnosed with nonfunctional tumors, a total of 30 received surgery in our hospital, 13 of whom had surgery due to the increasing size of the mass and concern for possible malignancy, seven of whom received surgery due to the size of tumor being greater than 4 cm even if HU was less than 10 on CT, and 10 of whom underwent adrenalectomy concurrent with surgery for other indications (lung lobectomy in one subject, cholecystectomy in three subjects, gastrointestinal tumor surgery in three subjects, hernia

surgery in one subject, and nephrectomy in two subjects).

RESULTS

Out of 348 patients, it was observed that 30 subjects (8.6%), 68 subjects (19.6%), 113 subjects (32.5%), 93 subjects (26.7%), and 44 subjects (12.6%) were, respectively, under age 40, between 40 to 50, between 50 to 60, between 60 to 70, and greater than 70 years old, indicating that the adrenal masses were most commonly detected in patients in their sixth or seventh decade. There were 156 males (44.8%) and 192 females (55.2%). It was observed that 216 subjects (62%), 105 subjects (30.2%), and 27 subjects (7.8%) had a mass discovered in the left adrenal gland, the right, and bilaterally, respectively, demonstrat-

ing a tendency of masses to be found on the left (Table 1).

It was observed 15 subjects (4.3%) had a mass of less than 1 cm, 303 subjects (87.1%) had a mass between 1 and 4 cm, and 30 subjects (8.6%) with over 4 cm of masses. The location, size, and shape of masses were determined by CT and it was found that 262 subjects, or 75.3% of the total masses, had features consistent with adenoma; 254, or 96.9% of those 262 subjects, were less than 4 cm in size. Additionally, 34 subjects (9.8% of 348 patients) had pheochromocytoma or malignant findings on pathology; of those, 13, or 38.2% of 34 patients, were over 4 cm in size. Myelolipomas, cysts, and other masses were detected in nine subjects (2.6%), five subjects (1.4%), and one subject (0.3%), respectively (Table 2). Measurement of HU by nonenhanced CT yielded 107 subjects (45.0%) and 58 subjects (24.4%) out of 238 patients with adenoma-like appearance with less than 10 HU and over 20 HU, respectively. Conversely, measurements of less than 10 HU and greater than 20 HU were observed in one subject (4.3%), and 19 subjects (82.6%) of the 23 patients with pheochromocytoma-like imaging, respectively, and in zero subjects and seven subjects (87.5%) of the eight patients with malignant characteristics on imaging, respectively, indicating that benign adenomas tended to have lower HU measurements (Table 3). Among the entire patient cohort, 62 patients (17.8%) possessed functional tumors; of them, pheochromocytoma, subclinical Cushing's syndrome, and aldosterone secreting adenoma were diagnosed in 40.3% ($n=25$), 33.9% ($n=21$), and 25.8% ($n=16$) of functional masses, respectively. Pheochromocytoma was the most common functional tumor observed. Of 69 subjects who un-

Table 1. Baseline Characteristics of 348 Adrenal Incidentaloma

Characteristic	No. (%)
Age, yr	
<40	30 (8.6)
≥40, <50	68 (19.6)
≥50, <60	113 (32.5)
≥60, <70	93 (26.7)
≥70	44 (12.6)
Sex	
Men	156 (44.8)
Women	192 (55.2)
Site	
Right	105 (30.2)
Left	216 (62.0)
Both	27 (7.8)

Table 2. Distribution of Clinical Diagnosis by Mass Size

Clinical diagnosis (n)	<1 cm (%)	≥1, ≤4 cm (%)	>4 cm (%)
Adenoma (262)	14 (4.0)	240 (69.0)	8 (2.3)
Subclinical Cushing's syndrome (21)	-	20 (5.7)	1 (0.3)
Primary aldosteronism (16)	-	15 (4.3)	1 (0.3)
Pheochromocytoma (25)	1 (0.3)	17 (4.9)	7 (2.0)
Malignancy (9)	-	3 (0.9)	6 (1.7)
Myelolipoma (9)	-	5 (1.4)	4 (1.1)
Cyst (5)	-	3 (0.9)	2 (0.6)
Other (1) ^a	-	-	1 (0.3)
Total (348)	15 (4.3)	303 (87.1)	30 (8.6)

^aOther, oncocytoma.

Table 3. Distribution of Clinical Diagnosis by Hounsfield Units

Clinical diagnosis (n)	<10 HU (%)	≥10, ≤20 HU (%)	>20 HU (%)
Adenoma (238)	107 (33.6)	73 (23.0)	58 (18.2)
Subclinical Cushing's syndrome (20)	12 (3.8)	4 (1.3)	4 (1.3)
Primary aldosteronism (14)	9 (2.8)	2 (0.6)	3 (0.9)
Pheochromocytoma (23)	1 (0.3)	3 (0.9)	19 (6.0)
Malignancy (8)	-	1 (0.3)	7 (2.2)
Myelolipoma (9)	9 (2.8)	-	-
Cyst (5)	-	2 (0.6)	3 (0.9)
Other (1) ^a	-	-	1 (0.3)
Total (318)	138 (43.4)	85 (26.7)	95 (29.9)

^aOther, oncocytoma.

Table 4. Characteristics of 69 Adrenal Incidentaloma with a Histopathologic Diagnosis Proven by Surgery

Histopathologic diagnosis (n)	No. of resection (%)			
	Size >4 cm	Functional mass	Suspected malignancy	Concomitant operation
Adenoma (35)	4 (5.8)	16 (23.2) ^a	8 (11.6)	8 (11.6)
Adrenocortical carcinoma (3)	-	-	3 (4.3)	-
Pheochromocytoma (17)	-	17 (24.6)	-	-
Cyst (4)	-	-	3 (4.3)	1 (1.4)
Myelolipoma (4)	-	-	3 (4.3)	1 (1.4)
Ganglioneuroma (4)	-	1 (1.4) ^b	3 (4.3)	-
Others (2) ^c	-	1 (1.4) ^d	1 (1.4)	-
Total (69)	4 (5.8)	35 (50.7)	20 (29.0)	10 (14.5)

^a16, 12 primary aldosteronism and 4 subclinical Cushing's syndrome; ^b1, subclinical Cushing's syndrome; ^cOthers: hematoma, necrotic nodule; ^d1, primary aldosteronism.

derwent adrenalectomy, adenoma was the most frequently observed, with 35 subjects (50.7%), followed by 17 subjects (24.6%) with pheochromocytoma, three subjects (4.3%) with primary adrenal cancer, four subjects (5.8%) with ganglioneuroma, four subjects (5.8%) with myelolipoma, and four subjects (5.8%) with cysts. A total of 35 subjects (50.7%) received surgery as treatment for functional tumors, followed by 20 subjects (29.0%) for masses concerning for possible malignancy, 10 subjects (14.5%) having adrenalectomy performed concurrently with surgery for nonadrenal conditions, and four subjects (5.8%) with a mass larger than 4 cm (Table 4).

DISCUSSION

According to other studies, adrenal incidentalomas are observed in approximately 6% of patients on autopsy [14]. Similarly, they are found in 4% of patients undergoing imaging with CT [2,15]. The prevalence of adrenal incidentalomas increases with age; the prevalence among people in their 20s and 30s is 0.2%, whereas it is about 7% in those over the age of 70 [16].

Regarding demographic characteristics, masses were most frequently found in patients in their sixth decade of life out of 348 subjects (32.5%), followed by the seventh decade (26.7%). This result is consistent with a previous study performed in another country, which found that the incidence increases with age and masses are infrequently observed in young and midaged adults [17]. However, incidence decreased in that cohort in people older than 70 (12.6%). This may be due to the fact that people in their 50s and 60s are more likely to have routine physical examinations, and have a high incidence of other

diseases as well. In addition, masses were more commonly found in females (55.2%) than males (44.8%). In some studies, such differences in gender distribution could be attributed to females having more opportunities to receive abdominal imaging and abdominal surgery compared to males. Other studies, however, have reported similar incidences of masses in males and females, based on autopsy findings [18,19].

In the present study, the masses were detected more frequently in the left adrenal gland (62.0%) compared to the right (30.2%), and occurred bilaterally in 7.8% of cases. Previous studies have not shown consistent results regarding the incidence of masses on either side. Most literature reports that approximately 10% of adrenal masses are detected bilaterally, which most commonly represents metastatic cancer or congenital adrenal hyperplasia [17,20]. Generally, these are defined as adrenal incidentalomas if size is greater than 1 cm [3]. It is also known that the specificity and sensitivity of a mass being malignant are 60% and 80% when it is larger than 4 cm [21]. In this study, 303 patients (87.1%) had a mass with size between 1 and 4 cm, thus, representing the highest frequency. Of them, 240 subjects (79.2%) and three subjects (1.0%) showed findings consistent with adenoma and malignancy, respectively, on imaging examinations; three subjects (26.7%) of the 30 with masses greater than 4 cm had findings consistent with adenoma. Surgical pathology was performed on 69 cases following adrenalectomy. While masses larger than 4 cm were found in all three patients (4.3%) with malignant findings, masses smaller than 4 cm were observed in all 35 patients (50.7%) with findings consistent with benign adenoma, indicating that larger masses were less likely to be benign. Moreover, similar results were reported in the previous studies

performed in Korea, as well as those from other countries, suggesting that the chances of having a malignant mass correlates directly with the size of the mass [3,10,22,23].

In addition to the size of tumors, HU measurement by non-enhanced CT can also be used as an indicator to differentiate between benign and malignant masses. HU is a unit that represents the dilution values of basic pixel in CT images via arbitrary numbers. It has been reported that the specificity of having a benign adenoma is close to 100% and the sensitivity is 85% when HU is less than 18. Clinically, benign masses are considered very likely when the HU measurement is less than 10, however, a reading of greater than 20 implies malignancy until proven otherwise [24]. In the present study, HU was measured in 238 patients who were considered clinically to have benign adenoma, based on laboratory and imaging findings; of those, there were 180 patients (75.6%) and 107 patients (45.0%) with HU readings of less than 20 and less than 10, respectively. In contrast, 19 subjects (82.6%) out of the 23 with pheochromocytoma-like findings and seven subjects (87.5%) out of the eight with malignant-like findings had high HU readings greater than 20. Therefore, when a mass is greater than 4 cm in size and HU is high (>20), it strongly suggests a diagnosis of malignant disease or pheochromocytoma.

Regarding the functionality of masses, it was observed that 62 (17.8%) patients of the entire 348-case cohort, had masses that were functionally active; of them, 25 patients (7.2%) had pheochromocytoma, similar to results published in another study, which reported approximately 8% in their series [20]. Among the functional tumors, pheochromocytomas were the most frequently observed in our review, followed by subclinical Cushing's syndrome (6.0%), and aldosterone secreting adenoma (4.6%), closely resembling the results of another study done in Korea [25]. A study from a different country, however, reported differing results, that subclinical Cushing's syndrome was found at the highest incidence among functional masses [17]. The higher incidence of aldosterone secreting adenomas in the present study compared to others could be explained by the fact that only one patient of the 13 diagnosed with aldosterone secreting adenoma upon screening underwent confirmatory test with physiological saline load test, while the remaining 12 were diagnosed via screening test only. The limitations of this study are: 1) the patients with hypokalemia were diagnosed with aldosterone secreting adenoma via screening only without confirmatory testing; and 2) the patients were diagnosed with subclinical Cushing's syndrome by 24-hour urinary free cortisol levels only, without an overnight dexametha-

sone (1 mg) suppression test.

Regarding malignant masses, findings consistent with malignancy were observed in nine of the total 348 subjects (2.6%), and primary adrenal cancer was diagnosed in three out of 69 subjects who received surgery (4.3%; 0.9% of the entire 348- patient cohort), consistent with previous studies done in other countries [1,14]. Adrenalectomy was carried out in 16 subjects with enlarging masses of the 262 who were diagnosed with adenoma on imaging; histologic examination of those showed 10 subjects with adenoma, three subjects with cysts, two subjects with ganglioneuroma, and one subject with hematoma. Changes in tumor size were not observed in most cases where characteristics of benign masses including adenoma were observed on imaging. This result was similar to studies done in other countries, so it is recommended that follow-up imaging be performed every 6 to 12 months for 3 to 4 years, based on the size of mass [18,24].

In conclusion, the characteristics of benign, malignant, non-functional, and functional masses of 348 patients with adrenal incidentaloma discovered in our hospital were similar to those reported in previous studies, with the exception that, among functional tumors, we found pheochromocytoma to be the most common, and a higher incidence of aldosterone secreting adenomas was also observed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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