Endocrine Journal 1995, **42** (4), 497–503

The Characteristics of Nine Patients with Adrenal Incidentalomas

NURI KAMEL, DEMET ÇORAPÇIOĞLU, ALI RIZA UYSAL, GÜRBÜZ ERDOĞAN, ALIM UZUNALIMOĞLU, NILGÜN BAŞKAL, AND MUSTAFA KEMAL BALCI

Ankara University, School of Medicine, Department of Endocrinology and Metabolic Diseases, Ankara, 06100, Turkey

Abstract. With the widening use of computerized tomography, the incidentaloma, an adenoma found incidentally in the adrenal, in computerized tomograms obtained for problems not necessarily related to the adrenal, has emerged as a recent clinical entity. Nine cases with such tumors are presented, here, along with a brief review of the related medical literature. Endocrine and other studies have shown that two of these nine patients had hormone secreting adrenal tumors, two pheochromocytomas. Surgical resection of the tumor was performed in six of the cases and aspiration biopsy was done in four with three completely benign cytological examination results (Class I or II) and one Class III result. The tumor with the class III result turned out to be a benign pheochromocytoma. CT estimates of the tumor size were 25 mm to 80 mm in the whole group and 30 to 80 mm in the patients who were operated on. Operation and histopathologic examination revealed three cortical adenomas, two pheochromocytomas, and one myelolipoma. Although no malignant tumors were found, the percentage of functioning adrenal neoplasms is rather high (22.2%) in this group of nine incidentalomas. Cases of adrenal incidentaloma therefore require a thorough endocrine evaluation along with other examinations which allow the clinician to follow tumor size.

Key words: Incidentaloma, Computerized tomography, Adrenal

(*Endocrine Journal* **42:** 497–503, 1995)

ADRENAL glands, due to their retroperitoneal location, are difficult to evaluate by physical examination and conventional radiological techniques. This has limited the detection of benign and malignant adrenal neoplasms to those tumors causing local symptoms due to massive enlargement or systemic manifestations of excess hormone production. However, at this stage, malignant tumors are often incurable, and hormone producing tumors have already caused substantial morbidity and even mortality. On the other hand, at present, technical advances make visualization of normal adrenal glands by ultrasound (USG) and computed tomography (CT) possible, and the possibility arises that adrenal neoplasms may be diagnosed at an earlier or even preclinical stage [1]. Treatment of these preclinically detected neoplasms would thus prevent the complications of hormone producing tumors and offer a better chance to cure malignant tumors [2]. This report describes our experience with nine patients in whom an adrenal mass was incidentally detected in an abdominal ultrasound or a CT scan obtained during a work up for an unrelated problem.

Received: February 23, 1994
Accepted: March 29, 1995
Correspondence to: Dr. Demet Çorapçioğlu, Dept. of Endocrinology and Metabolic Disease, Ankara University, School of Medicine, 06100 Samanpazari, Ankara, Turkey

Patients and Methods

At our department, the department of Endocrinology and Metabolic Diseases, Ankara University

Medical School, during a 24 month period beginning in September, 1991, eight patients with a unilateral adrenal mass as an incidental finding and one patient with bilateral adrenal masses, also an incidental finding, were identified. This group consisted of three men and six women who ranged in age from 49 to 66 years (mean, 48.7 years). The adrenal tumors were detected by USG or CT of the abdomen. None of the patients showed specific signs and symptoms of hormone excess. The reasons for performing the USG or the CT examination and CT findings related to the adrenal, in each patient, are shown in Table 1.

Upon detection of an adrenal mass, the patients were subjected to endocrine testing. Five of the nine patients had a history of hypertension. None had clinical findings, other than hypertension, suggesting pheochromocytoma, Cushing's syndrome, or a masculinizing or a feminizing syndrome. None had persistent hypokalemia. After an adrenal mass was noted in an ultrasound or CT scan, each patient was evaluated with respect to adrenal hormone secretion.

In addition to measurements of baseline plasma cortisol and urinary free cortisol levels, each patient was tested for pituitary-adrenal suppressibility by low dose dexamethasone (DXM) suppression tests (1 mg dexamethasone at night and 2 mg dexamethasone daily for two days). Daily excreted amounts of vanillymandelic acid (VMA) and metanephrine in urine were measured in each patient. Plasma renin and aldosterone levels both supine and following 4 h upright posture were also determined.

Serum cortisol and urinary free cortisol were measured by radioimmunoassay (RIA) (Amerlex RIA kit). Plasma adrenocorticotropic hormone (ACTH) was determined by RIA (RSL 125 IhACTH). VMA and metanephrine were determined in urine by chromatographic-spectrometric methods (Biosystems). Plasma aldosterone levels and plasma renin activity were also measured by RIA, using the DSL aldosterone RIA kit and the Sorin Biomedica kit respectively.

Radiological studies

CT scans were performed in 4 or 9 mm thick continuous slices before and after i.v. administration of contrast material.

Table 1. Data from patients with incidental asymptomatic adrenal masses

Patient no	Age (year)	Sex	Reason for CT or US	CT findings	Final diagnosis
1	50	M	Right upper quadrant pain	80 mm mass in right adrenal gland	Pheochromocytoma
2	61	F	Chronic lumbar pain	70 mm mass in right adrenal gland	Pheochromocytoma
3	55	M	Preoperative evaluation for thorax operation	30 mm mass in right adrenal gland	Nonfunctional adrenal mass
4	66	F	Chronic lumbar pain	35 mm mass in left adrenal gland	Adenoma originating in zona glomerulosa
5	58	F	Routine diagnostic research	70 mm mass in left adrenal gland	Adrenal cortical adenoma
6	49	F	High transaminases levels	40 mm mass in right adrenal gland	Adrenal cortical adenoma
7	40	F	Hypertension	60 mm mass in left adrenal gland	Myelolipoma
8	53	M	Possible metastatic malignancy	Multiple nodules in bilateral adrenal gland	Leiomyoma
9	51	F	Chronic abdominal pain (history of hypertension)	25 mm mass in right adrenal gland	Essential hypertension

CT, Computerized tomography of the abdomen; US, Ultrasonography of the abdomen.

Ultrasound

Ultrasonographic examinations were performed in all patients using Toshiba SAL 270 equipment with a 3.75 mHz probe.

Six out of nine patients were subjected to surgical exploration and six adrenal tumors were removed. All surgically removed tumors were available for histopathological studies. Light microscopy was performed using routine staining methods of paraffin embedded sections.

Results of preoperative clinical and endocrinological workup

Six of the patients were female (66.6%), and three male (33.4%). Generalized obesity was present in two patients (22.2%) and hypertension in five patients (55.5%). Three patients had non-insulin dependent diabetes mellitus (NIDDM) (33.3%).

Hormone values of our patients are shown in Table 2. Patients 1, 2, and 3 had elevated baseline plasma cortisol levels, and patients 1, 3, 5 and 6 had high urinary free cortisol excretion. However patients 1, 2, 3 and 6 maintained their diurnal rhythm of cortisol secretion and their morning plasma cortisol levels were suppressed completely on DXM. Patient 4 had high normal plasma cortisol with a normal diurnal rhythm of plasma cortisol levels. Her plasma cortisol level was suppressed by the 2 mg DXM test, but not by the overnight 1 mg DXM test. In another patient, patient 5, evaluation leads us to think that the patient might have had some form of a preclinical Cushing's syndrome. In the work-up before adrenalectomy, she had high daily free cortisol excretion and absence of diurnal variation in plasma cortisol levels. Her plasma cortisol concentration had not been suppressed by the 1 mg DXM test, but it had been normally suppressed by the 2 mg DXM test.

Two patients out of nine had hormone secreting adrenal tumors, phechromocytomas. These patients had increased urinary VMA (patients 1 and 2) or metanephrine (patient 2) excretions.

On CT images of adrenal glands, all patients had lesions of round shape around 2.5–8 cm in diameter, the mean tumor size being 32 mm. Tumor location was on the right side in 55.5% of the cases.

Fine needle aspiration of the adrenal mass was made in patients 2, 3, 4, and 5. The results are

Table 2. Endocrine findings in nine patients with adrenal masses

Patient no	Baseline cortisol 0800 h μg/dl (7–25)*	Baseline ACTH 0800 h pg/ml (10–100)*	Urinary cortisol excretion μg/24 h (35–120)*	Serum cortisol after 1 mg DXM at night μg/dl	Serum cortisol after daily 2 mg DXM μg/dl	Baseline plasma renin activity ng/ml/h (supine: 0.20–2.8)*	Baseline plasma renin activity ng/ml/h (upright: 1.5–5.7)*	Baseline aldosterone pg/ml (supine: 10–160)*	Baseline aldosterone pg/ml (upright: 40–310)*	VMA mg/24 h (3–9)*	Metanephrine (mg/24 h 0.0–1.0)*
1	27	44.6	140	1.6	23					12 10.6 2.4	0.5 0.6
2	28.3	90.5	53.9	1.8	1.4	0.7	1.6	221.3	49.2	16.0	2.4
3	34.20	16.3	123	3.7	4.1	0.16	0.18	17.5	110.6	4.4	0.18
4	24.5	40	47	19.3	1.5	6.0	2.4	187	120	9.0	0.97
5	20.5	52.0	151	25	2.1	1.1	1.8	118.7	97.7	5.8	0.3
6	20.1	30.6	130	1.8	5.3	0.05	0.11	31.9	208.6	4.6 6.5	1.0
7	24.7	31.3	58	2.7	3.5	0.8	0.84	385.5	436.2	3.2	0.91
8	13.0	58.8	32	4.8		0.82	0.61	132	62.8	3.3	0.26
9	10.0	29.7				0.1	0.9	59	219.3	5.1	0.07

*, Normal range at our laboratory; DXM, Dexamethasone; ACTH, Adrenocorticotropic hormone; VMA, Vanillymandelic acid.

Table 3. Operative and histological findings in patients with adrenal masses

Patient no	Operative findings	Tumor weight (g)	Cytology	Histopathology
1	70 mm adrenal mass	169		Pheochromocytoma
2	60 mm adrenal mass	103	Class III neoplasm	Pheochromocytoma
3			Class I	
4	30 mm adrenal mass	46	Class I	Adrenocortical adenoma
5	60 mm adrenal mass	98	Class II	Adrenocortical adenoma
6	40 mm adrenal mass	23		Adrenocortical adenoma
7	50 mm adrenal mass	45		Myelolipoma

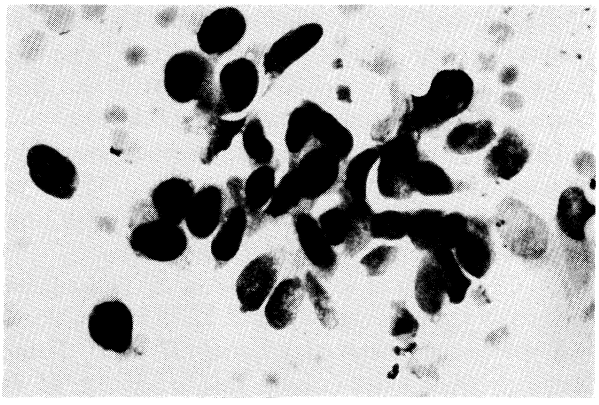

Fig. 1. Cells of polygonal or syncytial shape with eosinophilic granular cytoplasm contain a regularly round or oval nucleus. The cytological diagnosis is class III. Case 2 pheochromocytoma. May-Grünwald Giemsa, 400 ×.

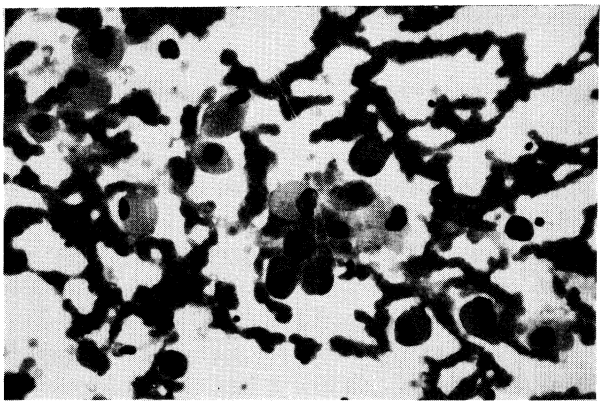

Fig. 2. Cells arranged in a trabecule or small cluster have homogenous and slightly basophilic cytoplasm and generally small round nucleus with a distinct nucleolus. The cytological diagnosis is class II. Case 5 adrenocortical adenoma. May-Grünwald Giemsa, 400 ×.

shown in Table 3. Cytological views of aspirates from 2 and 5 are shown in Figs. 1 and 2, respectively.

Pathological findings

Six patients were operated on. The results of pathological examinations of the removed tumors are shown in Table 3. The preoperative diagnosis of pheochromocytoma was supported in cases 1 and 2. Pathological specimens showed adrenocortical adenoma in three patients (33.3%), pheochromocytoma in two patients (22.2%) and myelolipoma in one patient (11.1%).

Postoperative course

All the six patients who underwent unilateral adrenalectomy followed an uneventful postoperative course without complications. In each case a mass similar in size and location to that noted on CT scan was found. Of these six, two were clearly accepted as nonfunctional: the cortical adenoma in patient 6 and the myelolipoma which was found in patient 7. Patients 1 and 2 had pheochromocytoma. After adrenalectomy, patient 4, who had, before the operation, hypertension, obesity, and NIDDM regulated with oral antidiabetic, no longer needed antihypertensives and his glycemia could be controlled with dietary measures alone. This patient was shown to have an adrenocortical adenoma (Table 3). In patient 5 who had signs, in the pre-operative endocrine work-up, suggesting the presence of a preclinical Cushing's syndrome, glycemic control and the management of hypertension remarkably improved following the extirpation of the cortical adenoma. After the operation, two patients with pheochromocytoma became normotensive without antihypertensive medication.

None of the patients developed adrenal insufficiency.

Discussion

With wider application of USG and CT, incidental adrenal tumors have been detected with increasing frequency. It is estimated that in approximately 0.6–9% of all abdominal CT's, clinically unsuspected adrenal tumors are discovered [3–5]. The majority of these tumors have been shown to represent stable or slowly growing adrenocortical adenomas, whereas metastases from occult malignancies, adrenomyelolipomas, pheochromocytomas, cysts, chronic granulomatous or inflammatory diseases, old adrenal hemorrhage [2, 6], and adrenocortical carcinomas are rarely found [3, 7]. With endocrine studies, most of these lesions have been shown to be nonfunctional [1]. However, some of the patients had asymptomatic pheochromocytomas [2] or asymptomatic aldosterone-producing tumors [1]. In addition, there have been several reports of incidentally detected cortisol-secreting adrenal tumors in otherwise healthy subjects [5, 8].

The incidence of functioning adrenal neoplasms is high in our rather small series. Incidental pheochromocytomas have been observed in 22.2% of our cases. Two of our patients had pheochromocytomas. Patient 1, with a pheochromocytoma, had also NIDDM and multinodular toxic goitre (MNTG), and he had no clinical findings suggestive of a pheochromocytoma. He had normal metanephrine excretion, but high VMA excretion as measured in two separate urine samples collected over a 24 h period (Table 2). Also the other patient with a pheochromocytoma, patient 2, had no clinical signs suggesting pheochromocytoma, but she had high VMA and metanephrine excretions. In both these cases, histopathology confirmed the preoperative diagnosis of pheochromocytoma. Apart from these two cases with definitely established pheochromocytomas, there are two other cases with features which strongly suggest the presence of a functional adrenal adenoma. The pathological examination of the excised material in patient 4, who had hypertension, revealed an adrenocortical adenoma. The plasma aldosterone level and the plasma renin activity of this patient were normal, but her cortisol secretion could only be suppressed by the 2 mg DXM test. Her plasma cortisol concentration was not suppressed by the overnight DXM test. Also in patient 5, though not definitely established, we strongly suspect the presence, before operation, of a cortisole producing adrenal adenoma, because this person had shown some of the important features of the preclinical Cushing's syndrome as defined by Reinke *et al.* [9]. Although her plasma cortisol level had been suppressed by the 2 mg DXM test, she had diabetes mellitus and hypertension along with the absence of a diurnal rhythm of cortisol secretion, excessive daily excretion of free cortisol, and absence of normal response to the 1 mg DXM test, and the management of her hypertension and diabetes remarkably improved following the excision of an adrenal cortical adenoma. Had their tumors been left untouched, these two cases, patients 4 and 5, might have developed full blown Cushing's syndrome in time, but we can never be sure.

In the face of the increasing incidence of incidentalomas, the question arises as to the clinical significance of these unsuspected adrenal masses. We do know from autopsy series that adrenal nodules are quite common. Adenomas of the adrenal cortex have been found in 1.45% to 33% of autopsies [10]. This wide range can be explained by the diligence of the investigator in looking for extremely small nodules and the fact that microscopic nodules were included in some series. Common and Callewas [11] found cortical adenomas greater than 3 mm in diameter in 2.8% of 9866 consecutive autopsies, while Kokko and coworkers [12] found cortical adenomas greater than 5 mm in diameter in 1.4% of 1495 consecutive autopsies. Up to 3% of normal adults may have macroscopic nodules in the adrenal gland [13]. Micronodular changes are seen in two thirds of normal adults [14]. Since adrenal masses smaller than 1 cm are unlikely to be identified by CT, the number of lesions a CT scan will detect should be much less than those detected in autopsy studies.

It is generally accepted that the small adrenal nodules found at autopsy do not have functional significance [15], but the same conclusion is not necessarily valid for larger lesions uncovered by CT. It is known that the number and size of adrenal nodules tend to increase with advancing age. Autopsy studies in older subjects have shown the highest frequency of adrenal nodularity. Dobbie

[16] has postulated that these nodules are part of the aging process, and has provided histological evidence suggesting that they are secondary to ischemia from vascular changes. A small nodule in an old patient is unlikely to be clinically significant. Thus, both the size of the lesion and the age of the patient are important considerations for evaluating incidental adrenal masses detected by CT scan. CT scan, or especially MRI, may be helpful in differentiating between adenomas, carcinomas, metastases, cysts, lipomas, myelolipomas, hemorrhage, chronic granulamatous and inflammatory diseases [17].

It is recommended that all patients with incidental adrenal nodules be screened for excess hormone production [3, 6]. This is certainly true for catecholamines and glucocorticoids, since our group and others have detected pheochromocytomas and preclinical Cushing's syndromes in such patients [1, 2, 18]. Of 72 patients with pheochromocytoma described by Modlin and associates [19], 14 were found unexpectedly at autopsy. Only 24% of 54 pheochromocytomas detected in autopsy at the Mayo Clinic were diagnosed during life [20].

Our present work-up of a patient with an incidental asymptomatic adrenal mass detected by a CT scan consists first of ruling out the possibility that it is a metastasis from another primary site. If this does not seem likely, screening for hypokalemia, and hormone production that is done by measuring urinary excretion of VMA, metanephrine, catecholamines, free cortisol, and by measuring plasma concentrations of cortisol, aldosterone, epinephrine, and norepinephrine are attempted. Care must be taken in the performance and interpretation of all these tests because they are suspectible to dietary, pharmacological, and environmental influences. Adrenal tumors picked up by incidental abdominal CT scans have been functional in less that 10% of the cases [4, 6]. Without rigid adherence to diagnostic techniques, it is easy to be misled into believing that a hormone producing tumor is present and that adrenalectomy is indicated [3].

If the hormone study results are negative, treatment must be individualized. In patients with an adrenal lesion greater than 3 cm in diameter, surgery may still be appropriate even if excess hormone production is not demonstrable [3, 6]. A mass smaller than 3 cm may be followed by a change in size on serial CT scans at intervals of 2, 6 and 18 months [6, 7]. An operation would be recommended only if growth is seen on serial examination of these nonfunctional lesions. Needle puncture of cysts may by appropriate, and clear fluid can be assumed to indicate a benign lesion. Bloody fluid warrants the same approach as for a small solid mass of similar size. Needle aspiration of a small solid mass may be considered, but the sensitivity of the cytological examination would be only 54% [6]. Moreover, the incidence of adrenocortical carcinoma among persons with small masses is less than 1 in 60 [21]. Therefore the likelihood of cytological findings positive for malignancy is less than 1% [6]. Needle aspiration of the lesion was performed in four of our cases. Three of these cases were later operated on. Of these three aspiration biopsies, two produced completely benign cytological results (classes I and II) which were verified by histology. In the third, the result was class III. In this patient, a benign pheochromocytoma was found. If an adrenal mass increases in size at any reevaluation, biochemical assessment should be repeated and surgery should be done. If its size is stable after 18 months, the mass can be left in place [6]. In patients who have known metastatic disease, or if the CT is consistent with an adrenal cyst or myelolipoma, no further diagnostic or therapeutic intervention is necessary [7]. This approach may be modified by future experience, but for now it suffices to prevent a substantial number of unnecessary operations.

Acknowledgement

We thank Dr. Cemil Ekinci of our cytology and pathology departments.

References

1. Kologlu S, Akyar S, Başkal N, Berk U (1988) Asymptomatic-nonfunctional adrenal masses detected by CT. *Rev Roum Med Endocrinol* 26: 173–178.
2. Prinz RA, Brooks MH, Churchill R, Graner JL, Lawrence AM, Paloyan E, Sparagana M (1992) Incidental asymptomatic adrenal masses detected by computed tomographic scanning. Is operation required? *JAMA* 248 (6): 701–704.
3. Thyrell JB, Aron DC, Forsham PH (1991) Glucocorticoids and adrenal androgens. In: Greenspan FS (ed) Basic and Clinical Endocrinology Appleton and Lange. 3rd ed: 323–362.
4. Glazer HS, Weyman PJ, Sagel SS, Levitt RG, McClennan BL (1982) Nonfunctioning adrenal masses: Incidental discovery on computed tomography. *AJR* 139: 81–85.
5. Ross N, Aron D (1990) Hormonal evaluation of the patient with an incidentally discovered adrenal mass. *N Engl J Med* 323: 1401–1405.
6. Copeland PM (1983) The incidentally discovered adrenal mass. *Ann Internal Medicine* 98 (6): 940–945.
7. Williams GH, Dluhy RG, Adams FD (1989) Diagnostic imaging of the adrenal gland. In: De Groot LJ (ed) Endocrinology. W.B. Saunders Company, 2nd ed, Volume 2: 1633–1646.
8. Beierwaltes WH, Sturman MF, Ryo U (1974) Imaging functional nodules of the adrenal glands with 131-I-19-iodocholesterol. *J Nucl Med* 15: 246–251.
9. Reinke M, Nieke J, Krestin GP, Saeger W, Allolio B, Winkelmann W (1992) Preclinical Cushing's syndrome in adrenal "Incidentalomas": Comparison with adrenal Cushing's syndrome. *J Clin Endocrinol Metab* 75 (3): 826–832.
10. Russi S, Blumenthal HT, Gray SH (1945) Small adenomas of the adrenal cortex in hypertension and diabetes. *Arch Intern Med* 76: 284–291.
11. Commons RR, Callaway CP (1948) Adenomas of the adrenal cortex. *Arch Intern Med* 81: 33–41.
12. Kokko JP, Brown TC, Berman MM (1967) Adrenal adenoma and hypertension. *Lancet* 1: 468–470.
13. Russell RP, Masi AT, Richter ED (1972) Adrenal cortical adenomas and hypertension. A clinical and pathological analysis of 690 cases with matched controls and a review of the literature. *Medicine* 51: 211–255.
14. Neville AM, O'Hare MJ (1985) Histopathology of the human adrenal cortex. *Clin Endocrinol Metab* 14: 791–820.
15. Kaplan NM, Cook R, Gulley S (1967) The steroid content of adrenal adenomas and measurements of aldosterone production in patients with essential hypertension and primary aldosteronism. *J Clin Invest* 46: 728–734.
16. Dobbie JW (1969) Adrenocortical nodular hyperplasia: The aging adrenal. *J Pathol* 99: 1–18.
17. Reining JW, Doppman JL, Dwyer AJ, Johnson AR, Knop RH (1986) Adrenal masses differentiated by MR. *Radiology* 158: 81–84.
18. Korobkin M, White EA, Kressel HY, Moss AA, Montagne J-P (1979) Computed tomography in the diagnosis of adrenal disease. *AJR* 132: 231–238.
19. Modlin IM, Farndon JR, Shepherd A, Johnston IDA, Kennedy TL, Montgomery DAD, Welbourn RB (1979) Pheochromocytomas in 72 patients: clinical and diagnostic features, treatment and long term results. *Br J Surg* 66: 456–465.
20. St John Sutton MG, Sheps SG, Lie JT (1981) Prevalence of clinically unsuspected pheochromocytoma: Review of a 50 year autopsy series. *Mayo Clin Proc* 56: 354–360.
21. Tang CK, Gray GF (1975) Adrenocortical neoplasms: prognosis and morphology. *Urology* 5: 691–695.