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ORIGINAL ARTICLE

Natural course of benign adrenal incidentalomas in subjects with extra-adrenal malignancy

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Abstract Patients with extra-adrenal malignancies are diagnosed increasingly with benign adrenal tumors, as well as non-oncology subjects. We aimed to demonstrate the natural course of adrenal adenomas in terms of mass size and hormonal status in oncology and non-oncology subjects. We also compared the characteristics and behavior of adrenal adenomas with adrenal malignancies. In our registry of adrenal tumors ($n = 335$), we prospectively evaluated 29 oncology subjects (EAM+) and age, gender, and follow-up duration matched 110 non-oncology subjects (EAM−) with adrenal adenomas. Median follow-up was 24 months. We also included 16 subjects with adrenal malignancies (primary; 3 and metastasis; 13). Tumor size was followed-up with CT or MRI at 6th and 12th months and annually in subsequent visits. Hormonal assessment was repeated at the 6th month after the initial visit and annually in subsequent visits. Initial tumor size, mean increase in tumor size, and number of subjects who showed mass enlargement or developed subclinical Cushing Syndrome were comparable ($P > 0.05$) between EAM+ and EAM− groups. Subjects with malignant adrenal tumors were older ($P = 0.06$), had larger tumors at presentation ($P < 0.001$), and showed mass enlargement during a shorter follow-up duration ($P < 0.001$). Oncology subjects with adrenal adenomas featured similar baseline and follow-up parameters in terms of mass enlargement and development of subclinical Cushing Syndrome when compared with non-oncology subjects. Malignant adrenal tumors were characterized with large, rapidly growing tumors of older ages. Conservative approach can be suggested to oncology subjects for adrenal adenomas unless clinical and radiological suspicion of adrenal malignancy is present.

Keywords Adrenal incidentaloma · Extra-adrenal malignancy · Follow-up

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Introduction

Incidentally discovered adrenal tumors have been increasingly recognized in radiological series due to the development of imaging techniques as well as repeated number of interventions [1]. In the literature, six computed tomography (CT) series recorded between 1982 and 1995 have demonstrated a mean prevalence 0.64% in 82,000 subjects, [1–7] while a recent study has observed that the overall prevalence of adrenal lesions was 4.4% [8]. Among incidentally discovered adrenal tumors, while non-functioning adenoma is the most common diagnosis; functioning adenoma, myelolipoma, cyst, primary adrenocortical carcinoma, or adrenal metastasis may also be demonstrated [1].

All kinds of radiological interventions are performed repeatedly and in large numbers in subjects with malignant diseases. The demonstration of an adrenal mass in oncology patients renders the exclusion of metastasis necessary. Adrenal gland is a common site of metastatic spread; especially from lung, breast, and kidney cancers. Lee et al. [9] demonstrated that adrenal gland was the site of metastasis at presentation in 5.8% of 1639 subjects with unknown primary cancer. Furthermore, it was shown that

overall survival was significantly shorter in patients with adrenal gland metastasis.

Adrenal tumors shown in patients with a history of malignancy are not always considered a true incidental finding because of the targeted radiological interventions required to perform a proper staging. However, in addition to non-oncology subjects, patients with extra-adrenal malignancies are diagnosed increasingly with benign adrenal tumors because of the developments in radiological techniques.

The available data on the natural course of benign adrenal lesions in oncology patients are scanty. In their recent retrospective study, Tsvetov et al. [10] demonstrated that during a 24-month median follow-up, tumor growth was significantly more common in oncology subjects.

The objective of our prospective study is to demonstrate the natural course of adrenal adenomas in terms of mass size and hormonal status in oncology and non-oncology subjects in a short follow-up duration. We also compared the characteristics and behavior of adrenal adenomas with adrenal malignancies.

Results

In our series, among 335 subjects who were referred because of incidentally discovered adrenal tumors, overall rate of metastatic adrenal lesion was 3.8%. Among 47 subjects with extra-adrenal malignancies, the rate of metastatic adrenal mass was 27.6% (13/47).

The demographic characteristics of the subjects prospectively evaluated are shown in Table 1. There was no significant difference regarding age, gender, median tumor size, and the number of bilateral tumors between EAM (+) and EAM (−) groups. Median follow-up duration was 31 months in EAM (+) group and 24 months in EAM (−) group ($P > 0.05$). The number of subjects who featured mass enlargement during follow-up was not significantly different among groups. Besides, the extent of mass enlargement and average mass enlargement (extent of mass enlargement/median follow-up) were also similar ($P > 0.05$).

In subjects with adrenal adenoma (EAM (+) + EAM (−), $n = 139$) subclinical Cushing Syndrome prevalence at presentation was 20.1% (28/139). The prevalence of subclinical Cushing Syndrome at presentation was comparable in the two groups. During follow-up, no new case of Cushing Syndrome, primary hyperaldosteronism, or pheochromocytoma was diagnosed; while one subject from EAM(+) group and seven subjects from EAM(−) group developed subclinical Cushing Syndrome (3.4% vs. 6.3%, $P > 0.05$).

We also compared the data of subjects diagnosed with adrenal adenomas (EAM (+) + EAM (−), $n = 139$) to those diagnosed with malignant adrenal tumors (primary $n = 3$ + metastasis $n = 13$). Subjects with malignant adrenal tumors were slightly older at diagnosis ($P = 0.06$).

Table 1 Prospective evaluation of participants and characteristics of their adrenal tumors

	Adrenal adenoma ($n = 139$)		P^c +vs−	Malignant adrenal mass ($n = 16$)		P^c A vs. M
	EAM (±) ($n = 29$)	EAM (−) ($n = 110$)		Primary[a] ($n = 3$)	Metastasis[b] ($n = 13$)	
Age	54.2 ± 11.6	57.3 ± 11.5	ns	59.6 ± 7.2	62.4 ± 18.1	0.060
Gender (M/F)	6/23	32/78	ns	1/2	12/3	<0.001
Median tm size (mm)	21 (8–60)	20 (7–60)	ns	85 (80–90)	25 (10–70)	0.011
Bilateral (*n*)	6	17	ns	–	5	ns
sCS (*n*)	3	25	ns	1	–	–
Follow-up data						
Duration (month)	31 (8–72)	24 (6–159)	ns	6	11.5	ns
Increase in size (*n*)	3	24	ns	1	2	<0.001
Enlargement (mm)	7.3 ± 2.51	6.25 ± 3.66	ns	60	40.0 ± 14.14	<0.001
Average enlargement (Enlargement/duration)	0.23 ± 0.20	0.32 ± 0.58	ns	10	3.44 ± 1.01	<0.001
Adrenalectomy	1	5	ns	3	11	<0.001

Results are expressed as mean ± SD or median (range)

EAM extra-adrenal malignancy, *tm* tumor, *sCS* subclinical Cushing Syndrome, *ns* not significant

[a] There were two patients with malignant pheochromocytomas and one subject with primary adrenocoritcal carcinoma. Malignant pheochromocytomas were operated at diagnosis. Follow-up data correspond to the subject with adrenocortical carcinoma

[b] Follow-up data are associated with two subjects

[c] Note that the first *P* values demonstrate EAM(−) vs. EAM(+); the second *P* values demonstrate adrenal adenoma (A) vs. malignant adrenal mass (M)

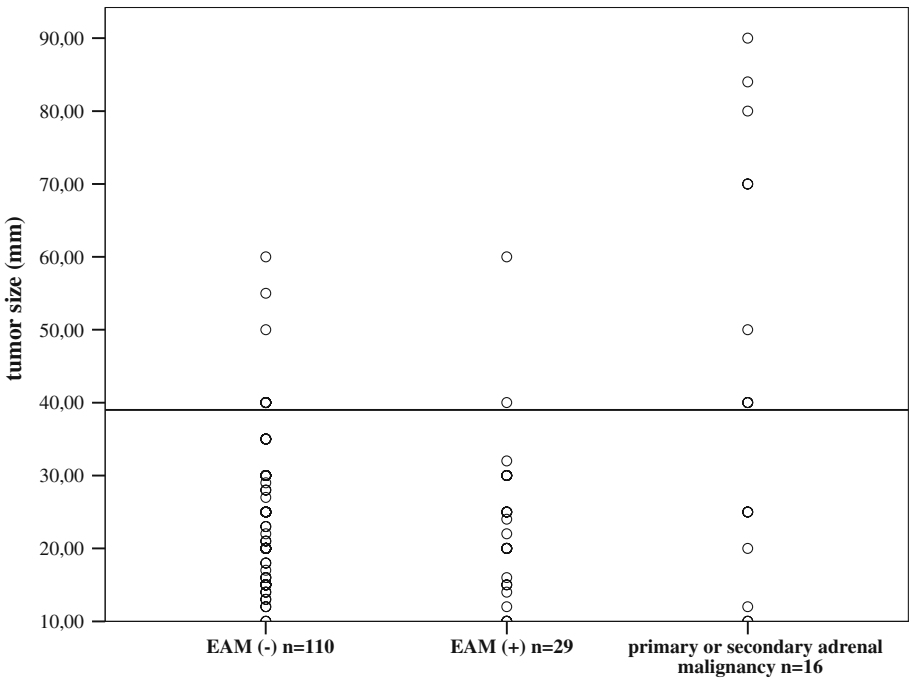

Fig. 1 Distribution of subjects regarding tumor size in groups EAM; extra-adrenal malignancy. Flat line represents 4 cm; which has been suggested as the absolute tumor size for surgery

Female–male ratio was 2.6 in adenoma group versus 0.4 in malignant adrenal tumors group ($P < 0.001$). Bilateral adrenal tumors were insignificantly more common in malignant adrenal tumor group. Number of subjects who featured mass enlargement, extent of mass enlargement, and average enlargement were significantly higher in malignant adrenal tumor group ($P < 0.001$ for each).

Distribution of tumor size in groups is demonstrated in Fig. 1. Tumors equal or smaller than 20 mm were 56 (49.6%), 15 (51.5%), and four (25.1%) subjects in EAM (−), EAM (+), and M groups, respectively. In EAM (−) group, 10 (9.1%) subjects had 40 mm or larger tumors, whereas two subjects (6.8%) in EAM (+) group, and nine subjects (56.2%) in M group had 40 mm or larger tumors.

Adrenalectomy was suggested to one subject in EAM (+) group due to change in radiological characteristics of the mass without mass enlargement. Five subjects required adrenalectomy in EAM (−) group: owing the mass enlargement in one subject, because of the effects of subclinical Cushing Syndrome in two subjects, and owing to the change in radiological characteristics of the mass without mass enlargement in two subjects. Pathological diagnosis revealed adrenal adenoma in all the patients.

Discussion

Subjects with any kind of malignancy experience an increase in the number of radiological interventions, which has led to an increase in the detection rate of adrenal tumors. However, current data regarding the natural history of adrenal adenomas in oncology subjects are scanty. Previous studies have shown that, in oncology subjects, 50–70% of the adrenal tumors were due to metastasis [11, 12]. Nevertheless, in a more recent study, probably related with the increase in the determination of smaller and benign adrenal lesions, one subject with adrenal gland metastasis was described among 100 consecutive patients with incidentally discovered adrenal tumors [10]. In our series, overall metastasis rate and rate of metastatic adrenal lesions in oncology subjects are 4 and 27%, respectively. The variations between our results and those previously reported may be associated with the diversity in number of participants. Radiological assessment bias should also be considered. None of our patients was diagnosed or followed up with ultrasonography. Ultrasonography may not detect smaller lesions. Furthermore, left adrenal masses may not be recognized because of the difficulties in visualization [13]. Another important issue could be referral bias. It is conceivable to estimate that not all the oncology subjects with adrenal tumors have been referred to endocrinology departments.

The data regarding prospective evaluation of adrenal adenomas in oncology subjects are not satisfactory. Recently, Tsvetov et al. [10] demonstrated that, after 24 months follow-up, the extent of tumor enlargement and functional abnormalities were comparable between oncology and non-oncology subjects while the percent of subjects featuring tumor growth was higher in oncology subjects. In this study, we have shown no significant difference regarding initial tumor size, number of subjects regarding mass enlargement, extent of mass enlargement, and average mass enlargement

between oncology and non-oncology subjects. In Tsvetov's study, we suggest that inclusion of significantly older patients in oncology subjects group led to the finding of increased frequency of mass enlargement. In autopsy studies, it was demonstrated that occurrence of adrenocortical nodules increased with age [13]. Considering this limitation, we included age-matched non-oncology subjects, and showed similar tumor enlargement.

The comparison of adenoma group and malignant adrenal tumor group has yielded anticipated findings. Malignant adrenal tumors were both larger at presentation and also featured significant enlargement during shorter follow-up. Demographic characteristics showed older subjects with male dominance. Current guidelines about management of adrenal lesions suggest lesion size as one of the most important factors for the prediction of tumor's nature. It has been shown that the risk of malignancy increased significantly in lesions larger than 4 cm [11, 14]. Our findings were partially parallel with those observations. We showed that just 16% of benign, but 56% of malignant adrenal tumors were 4 cm or larger. It must be noted that all the three subjects with primary adrenal malignancies had 4 cm or larger tumors while metastatic lesion size varied between 10 and 70 mm. It may be suggested that considering 4 cm as an absolute cut off for surgery may not be convenient for all oncology patients with adrenal tumors; smaller lesions may also be metastasis. Radiological appearance of the tumor can be more helpful in such cases.

The most common hormonal disturbance in adrenal adenomas is subclinical Cushing Syndrome which was defined as the subtle cortisol autonomy without the clinical characteristics of hypercortisolism [15]. The prevalence varies between 5 and 40% owing to the different criteria being used to detect cortisol autonomy [1]. Tsvetov et al. [10] have demonstrated that subclinical Cushing syndrome prevalence was 7.4% in their series with no difference between oncology and non-oncology subjects. In our study, overall prevalence and prevalence in oncology group was 20 and 10%, respectively. The variations between reported rates may be associated with the use of different diagnostic criteria. Tsvetov et al. defined subclinical Cushing Syndrome without assessing midnight cortisol. Besides, they preferred 5 μg/dl as the cut-off value in 1 mg DST, which might be associated with not only less false positive but also more false negative subjects.

During follow-up, overall rate of subclinical Cushing Syndrome development was 5.7% with no significant difference between oncology (3.4%) and non-oncology (6.3%) subjects. In a recent study, Barzon et al. [1] demonstrated that estimated cumulative risk of subclinical glucocorticoid production was 3.8% after 1 year and 6.6% after 5 years in non-oncology subjects. Interestingly, Tsvetov et al. [10] did not observe any new cases of subclinical Cushing syndrome in oncology or non-oncology subjects after 24 months of follow-up probably related with their diagnostic criteria.

It must be noted that subclinical Cushing syndrome is generally a laboratory diagnosis. Acute and chronic stress, which is associated with the course of malignancy, may alter hypothalamic–pituitary–adrenal axis [16]. Animal studies also showed that acute or chronic stress caused several disturbances regarding hypothalamic–pituitary–adrenal axis [16–19]. This should be considered during the evaluation of oncology subjects in order to prevent overdiagnosis of subclinical Cushing Syndrome.

In conclusion, oncology subjects with adrenal adenomas featured similar baseline and follow-up parameters in terms of mass enlargement and development of subclinical Cushing Syndrome when compared to non-oncology subjects. Malignant adrenal tumors were characterized with large; rapidly growing tumors of older ages. In cases where clinical or radiological suspicion of adrenal malignancy is not present, conservative approach for adrenal lesions can be suggested for oncology subjects.

Materials and methods

This study was conducted in Division of Endocrinology and Metabolism, Dokuz Eylul University. Ethical committee of Dokuz Eylul University approved the study.

All the subjects who were referred to our institute with incidentally discovered adrenal tumors since 2002 have been recorded. The number of subjects in the registry was 335 in January 2009. The distribution and baseline characteristics of the subjects according to the diagnosis are demonstrated in Table 2. Among participants, extra-adrenal malignancy prevalence was 14% (47/335) and primary adrenal malignancy rate was 0.9% (two malignant pheochromocytomas and one adrenocortical carcinoma). Adrenal gland metastasis was found in 3.8% (13/335) subjects (non-small cell lung cancer = 7, renal cell carcinoma = 3, non-Hodgkin Lymphoma = 2, and pancreas carcinoma = 1). Metastasis was diagnosed histologically in 12 patients (adrenalectomy ($n = 7$), CT-guided biopsy ($n = 5$)). One subject with non-small cell lung carcinoma had typical bilateral metastatic adrenal masses; thus adrenal biopsy was not performed.

Initial radiological examination was through CT in study participants. Radiological follow up was performed with CT and/or magnetic resonance imaging (MRI) at the 6th and the 12th months, and annually in subsequent visits. Malignancy was excluded if the following criteria were met in CT: (i) regular shape with well-defined margins and homogenous, (ii) attenuation value of 10 or less Hounsfield units on unenhanced CT scan, and (iii) 30 or less

Table 2 Distribution and characteristics of incidentally discovered adrenal tumors in the registry ($n = 335$)

Diagnosis	NFA	sCS	PHE	CS	Other[a]	Metastasis	PHA
No. of subjects	$n = 217$	$n = 45$	$n = 19$	$n = 16$	$n = 15$	$n = 13$	$n = 10$
%	64.5	13.5	5.7	4.8	4.5	4	3
Age	56.2 ± 12.1	59.6 ± 10.8	46.0 ± 12.7	40.7 ± 13.2	43.3 ± 18.1	62.4 ± 18.1	50.4 ± 11.3
Gender (M/F)	61/154	9/36	9/10	1/15	5/10	12/3	2/8
Tm size (mm)	20 (8–60)	25 (7–55)	50 (25–97)	35 (20–60)	40 (20–70)	25 (10–70)	11 (7–20)
Bilateral (*n*)	32	10	2	1	–	5	–
Primary adrenal malignancy (*n*)	–	1	2	–	–	–	–
Extra-adrenal malignancy (*n*)	28	3	1	1	1	13	–

Results are expressed as mean ± SD or median (range)

NFA non-functioning adenoma, *sCS* subclinical Cushing Syndrome, *PHE* pheochromocytoma, *CS* Cushing Syndrome, *PHA* primary hyperaldosteronism, *tm* tumor

[a] myelolipoma ($n = 9$), adrenal cyst ($n = 6$)

Hounsfield units on enhanced CT scan. Magnetic resonance imaging was performed when CT scan failed to confirm the diagnosis. In addition, MRI was preferred in cases of hypersensitivity history to non-ionic iodinated contrast medium or history of impaired renal function.

In non-oncology subjects, adrenalectomy was suggested in case of rapid growing tumors without benign appearance in CT or MRI or diagnosis or development of clinically overt hormone hypersecretion. In oncology subjects, adrenalectomy or CT-guided biopsy was suggested in case of malignant appearance in CT or MRI.

Hormonal evaluation was performed at 6 months after the initial visit, and annually in subsequent visits. Hormonal evaluation included 8.00a.m. cortisol, dehydroepiandrosterone sulfate (DHEA-S), adrenocorticotrophic hormone (ACTH), and in hypertensive subjects, plasma renin activity and serum aldosterone. Subsequently, urinary-free cortisol (UFC) (normal range <110 μg), urinary normetanephrine (normal range: 88–444 μg/day), and urinary metanephrine (normal range: 52–341 μg/day) were measured and overnight 1 mg dexamethasone suppression test (DST) was performed.

The suppression in overnight DST was adequate when morning cortisol fell below 1.8 μg/dl. When post-DST cortisol was over 1.8 μg/dl, 2-day 2 mg dexamethasone suppression test involving the administration of 0.5 mg oral dexamethasone given every 6 h for 48 h was performed. In subjects with non-suppressed cortisol levels, diurnal rhythm of cortisol was also evaluated (normal: midnight cortisol <7.5 μg/dl). Subclinical Cushing Syndrome (sCS) was defined if post-DST cortisol >1.8 μg/dl and at least one of the following conditions was positive; ACTH <5 pg/ml, UFC >110 μg/day, or midnight cortisol >7.5 μg/dl.

Pheochromocytoma was defined with elevated levels of urinary normetanephrine and/or metanephrine. Primary hyperaldosteronism was screened in hypertensive subjects with aldosterone/plasma renin activity ratio (ARR). In subjects with ARR > 25, saline infusion test was performed. Adrenal vein sampling was performed in one subject.

Among subjects with extra-adrenal malignancy (EAM (+) group, $n = 47$), we excluded subjects with metastatic adrenal tumors ($n = 13$), adrenalectomized subject with Cushing Syndrome ($n = 1$) and pheochromocytoma ($n = 1$), adrenal myelolipoma ($n = 1$), and subjects with inappropriate data ($n = 3$) from the follow-up. The distribution of primary malignancy sites among remaining 29 oncology patients with adrenal adenomasis given in Table 3. We compared these patients' data with subjects without known malignancy (EAM (−) group, $n = 110$). For this purpose, we included age, gender, and follow-up-duration-matched 110 subjects with non-functioning adrenal adenomas from our registry.

Table 3 Distribution of primary malignancy sites in prospectively evaluated subjects

Number of subjects ($n = 29$)	Primary malignancy site
7	Hematologic malignancy
5	Ovarian tumor
2	Prostate carcinoma
2	Multiple endocrine neoplasia
2	Non small cell lung cancer
2	Stomach
2	Breast
2	Thyroid papillary carcinoma
1	Thyroid papillary carcinoma + pulmoner carcinoid
1	Thyroid papillary carcinoma + endometrium carcinoma
1	Brain
1	Skin
1	Bladder

We also compared the demographic characteristics and follow-up data of adrenal adenomas (EAM (+) + EAM (−), $n = 139$) with malignant adrenal tumors (primary, $n = 3$ + metastasis, $n = 13$). Primary adrenal malignancies were primary adrenocortical carcinoma in one subject and malignant pheochromocytoma in two subjects. The patient with primary adrenocortical carcinoma was a 68-year-old female who presented with a 24-mm adrenal tumor and subclinical Cushing Syndrome. Her adrenal mass became 85 mm in 6 months, and she was diagnosed with primary adrenocortical carcinoma after adrenalectomy. Among 13 patients with adrenal gland metastasis, two were prospectively evaluated during a median duration of 11.5 months and then operated. Pathological diagnosis was achieved in the remaining 11 subjects at presentation. Thus, three subjects in malignant adrenal tumors group had follow-up data.

At presentation, there were no cases of pheochromocytoma, Cushing Syndrome, or PA in EAM (+) or EAM (−) groups. In malignant adrenal tumor group, there were two cases with malignant pheochromocytoma. Subclinical Cushing Syndrome was shown in 3 (10.3%) cases in EAM (+) group, 25 (22.7%) cases in EAM (−) group and also in the subject with primary adrenocortical carcinoma.

Cortisol, DHEAS and ACTH were measured using chemiluminescence enzyme immunoassay kits (Immulite, Diagnostic Products Corporation, Los. Angeles, USA). Plasma renin activity and aldosterone were measured using radioimmunoassay kits. Urine-free cortisol and metanephrines were measured by high performance liquid chromatography (Agilent Technologies, Santa Clara, USA).

Statistical analysis was performed with SPSS V 15.0. Each continuous variable was assessed with Kolomogorov–Smirnov Test. Variables with normal distribution were expressed as mean ± standardized deviation (SD). Median and range were given for the variables without normal distribution. Related samples were compared with Mc-Nemar Test for dichotomous variables. Wilcoxon Test or Paired Samples *t*-Test was performed for continuous related samples. Comparisons between groups were performed with Chi-square test for dichotomous variables. Independent Samples *t*-Test or Mann–Whitney *U* Test was used according to the distribution to evaluate continuous variables.

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