CLINICAL STUDY

Long-term follow-up study of patients with adrenal incidentalomas

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Abstract

Background: The incidence of adrenal incidentalomas has sharply increased in recent decades and concurrent subtle endocrine abnormalities, or even subclinical conditions, have been identified. Nonetheless, data concerning possible changes in adrenal size and/or hormonal pattern during follow-up are still inadequate.

Objective: To evaluate long-term morphological and functional evolution of adrenal incidentalomas after initial diagnosis and to identify possible risk factors for hormonal hyperactivity and mass enlargement.

Patients: Sixty-four patients (34 – 79 years) were followed-up for 12 – 120 months (median 25.5 months). Initial computerized tomography scan showed a unilateral mass in 51 patients and bilateral lesions in 13 patients. Average mass diameter at diagnosis was 2.5\textsuperscript{0.1} cm (range 1.0 – 4.0). Twelve patients had subclinical Cushing’s syndrome, 41 had mild hormonal alterations, and 11 had normal adrenal function at baseline. All patients were investigated by morphological and functional evaluation 6 and 12 months after diagnosis, and then at 1-year intervals.

Results: During follow-up, a mass size increase \(\geq 1\) cm was observed in 13 patients, and 18 developed further subtle endocrine alterations. Cumulative risk of developing endocrine abnormalities was 17% at 1 year, 29% at 2 years, and 47% at 5 years. The risk was higher in the first 2 years of follow-up if the initial tumor diameter was \(\geq 3\) cm. Overall, cumulative risk of mass enlargement was 6% at 1 year, 14% at 2 years, and 29% at 5 years, and it was greater in patients with normal adrenal function than in those with subtle hormonal abnormalities \((P < 0.05)\). One female subject showed a mass enlargement after 6 months of follow-up and was eventually diagnosed with non-Hodgkin’s lymphoma.

Conclusions: Patients with an adrenal incidentaloma are at risk for tumor growth and development of hormonal alterations. The risk of adrenal malignancy, although not elevated, also indicates the need for long-term follow-up.

European Journal of Endocrinology 147 489–494

Introduction

Adrenal incidentalomas are masses of 1 cm or more in diameter, discovered incidentally during imaging investigation of non-adrenal disorders. This clinical condition is frequently diagnosed and its prevalence ranges between 1 and 5% in different series (1 – 3). Adrenal incidentaloma has been associated with subtle endocrine abnormalities, such as low dehydroepiandrosterone sulfate (DHEA-S) levels, and increased 17-hydroxyprogesterone (17-OHP) and 11-deoxycorticisol responses to adrenocorticotropin (ACTH) administration (4 – 9). Silent pheochromocytomas and subclinical Cushing’s syndrome (SCS), which is characterized by autonomous cortisol-secreting adenomas without signs or symptoms of hypercortisolism, were also found, albeit less frequently (9 – 13).

The type and the frequency of endocrine and imaging investigations to be performed during follow-up remain controversial, because data on possible adrenal size increase and hormonal pattern changes over time are still inadequate. The incidence of either mass enlargement or hormonal alterations during long-term follow-up has not been thoroughly investigated. Recently, Barzoni et al. (14) evaluated long-term clinical, hormonal, and morphological outcomes in patients with adrenal incidentalomas in order to obtain prognostic factors for disease progression.
The aim of this retrospective study was to evaluate the cumulative risk of developing endocrine abnormalities and of mass enlargement, as detected by computerized tomography (CT), in a group of patients with incidentalomas with a minimum follow-up of 12 months.

**Subjects and methods**

Sixty-four patients (forty females, median age = 61 years, range 39–79; twenty-four males, median age 59.5 years, range 34–76) were followed up for 12–120 months (median = 25.5 months). Adrenal masses were discovered incidentally through imaging techniques performed for the evaluation of unrelated disorders. CT scan demonstrated a unilateral mass in fifty-one patients (thirty-two in the right gland and nineteen in the left), and bilateral lesions in thirteen, the mean diameter being $2.5 \pm 1.0$ cm (range 1.0–4.0). Thirty-eight patients had a lesion < 3 cm, and twenty-six ≥ 3 cm. In forty-two patients ultrasonography (US) was also performed: US mass size was concordant with CT measurement in only 55% of cases. In these patients, the mean diameter was $26.7 \pm 1.6$ mm at US, and $26.8 \pm 1.4$ mm at CT scan. A close correlation was found between US and CT measurements of mass size ($r = 0.65, P < 0.0001$). Hypertension was present in 55% of the cases, overt type-2 diabetes mellitus in 22%, and overweight in 31%. During follow-up, additional patients developed high blood pressure ($n = 4$), type-2 diabetes mellitus ($n = 1$), and overweight ($n = 10$). Three of these patients showed a concurrent mass enlargement ≥ 1 cm.

The following hormonal determinations were performed in all patients by commercial kits, as previously reported (6): plasma ACTH and serum cortisol, 17-OHP, DHEA-S, Δ4-androstenedione and testosterone levels, plasma renin activity and aldosterone in supine and upright positions, 24-h urinary free cortisol (UFC) and catecholamine excretion. Serum cortisol and 17-OHP levels were also measured before and after exogenous ACTH injection (250 μg i.v.). ACTH and cortisol levels were also evaluated after an overnight 1 mg dexamethasone test. In patients with SCS, cortico-

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**Figure 1** Frequency of hormonal abnormalities in 12 patients with subclinical Cushing’s syndrome (group A) at first presentation and during follow-up, in both basal and dynamic conditions. Dexa, dexamethasone; UFC, urinary free cortisol; ACTH, adrenocorticotropic; CRH, corticotropin-releasing hormone.
tropin-releasing hormone (CRH; 1 μg/kg i.v.) and loperamide tests (16 mg orally) were also performed.

As previously reported (6, 9, 10), SCS was defined by the absence of signs or symptoms of hypercortisolism and by the presence of at least two of the following criteria: inadequate cortisol inhibition after 1 mg dexamethasone (cortisol levels ≥ 138 nmol/l), high or high-normal UFC excretion (≥ 275 nmol/24 h), low or low-normal plasma ACTH levels (< 0.7 pmol/l), blunted ACTH increase after CRH test (< 4.4 pmol/l), and lack of cortisol suppression after opioid agonist loperamide administration (≥ 138 nmol/l).

The patients were reinvestigated at 6 and 12 months and then yearly, by clinical examination, routine chemistry, hormonal determinations in basal and dynamic conditions, and by CT scan. During the follow-up the mass was defined as enlarged when the increase was equal or more than 1 cm.

**Statistical analysis**

The Kaplan–Meier method was used to estimate the cumulative risk of endocrine abnormalities and mass enlargement during follow-up. The Wilcoxon (Breslow) test for equality of survivor functions was used for group comparisons. The Bonferroni correction for multiple comparisons was implemented, if needed. We used simple regression analysis to assess between-variable correlation. \( P \) values < 0.05 were considered significant.

**Results**

At diagnosis, twelve patients had SCS (group A): eleven out of twelve patients showed a lack of cortisol suppression after dexamethasone, four out of twelve had high UFC, five out of twelve had low plasma ACTH levels, and three out of six had blunted ACTH responses to CRH. Inadequate inhibition to opioid agonist loperamide was found in six out of ten cases (Fig. 1). In addition, nine patients had low DHEA-S levels, and eleven showed 17-OHP hyper-response to ACTH stimulation (peak ≥ 15 nmol/l). Fifty-two patients had a non-functioning adrenal mass. Forty-one of them showed mild hormonal alterations (group B): high 17-OHP peak after ACTH test was found in thirty-four patients, DHEA-S levels were low in twenty-nine patients, UFC excretion was high in two cases, and plasma ACTH was low in two additional cases. One patient showed inadequate cortisol suppression after 1 mg dexamethasone. No endocrine abnormalities were detected in the remaining eleven patients with a non-functioning adrenal mass (group C).

SCS persisted throughout the follow-up in all twelve group A patients: a lack of cortisol suppression after dexamethasone was confirmed in eleven cases, increased UFC excretion in seven and low basal ACTH in six cases; we found blunted ACTH responses to CRH in five out of seven cases, and inadequate inhibition to loperamide in five out of six cases.

![Figure 2](https://www.eje.org)

**Figure 2** Estimated cumulative risk of developing endocrine abnormalities according with the mass size (< or ≥ 3 cm) in patients with adrenal incidentalomas.
None of the patients developed overt Cushing's syndrome. Twelve out of forty-one patients with mild hormonal alterations subsequently developed further endocrine abnormalities, but no subject developed SCS. In particular, a high 17-OHP peak after ACTH test was found in one patient, DHEA-S levels were low in three patients, plasma ACTH was decreased in four other cases and a lack of cortisol suppression after 1 mg dexamethasone was observed in four patients. Moreover, DHEA-S levels were low in three of the eleven patients with normal adrenal function at diagnosis.

In order to estimate the cumulative risk of developing endocrine abnormalities, Kaplan–Meier curves were created. Data after 5 years were not analyzed owing to the small number of patients. When the whole group of patients was considered, the risk of developing additional endocrine abnormalities was 17% at 1 year, 29% at 2 years, 39% at 3 years, 39% at 4 years, and 47% at 5 years. When subjects were divided by mass size at diagnosis, the risk of further endocrine changes in the first 2 years of follow-up was higher in patients with mass size ≥3 cm than in those with mass size <3 cm (23% vs 13% at 1 year, and 39% vs 24% at 2 years respectively). However, no overall significant difference between risk-curves was observed (Fig. 2).

As far as the mass size is concerned, lesion diameter at initial presentation was <3 cm in thirty-eight patients and ≥3 cm in twenty-six patients. Group A patients had a larger mass size though than groups B and C (2.8±1.0, 2.4±0.9, and 2.4±0.9 cm respectively), but these differences were not statistically significant. Morphological follow-up by CT scan showed the presence of adrenal mass enlargement ≥1 cm in thirteen cases (20%), four of whom had SCS. The average size increment was 1.7±0.2 cm. No patient showed a tumor reduction or disappearance during follow-up.

When all patients were considered, cumulative risk of developing mass enlargement (i.e. diameter increase ≥1 cm) was 6% at 1 year, 14% at 2 years, 17% at 3 years, 22% at 4 years, and 29% at 5 years. Figure 3 shows the risk of mass enlargement in patients with SCS, subtle endocrine abnormalities, or without any hormonal alteration. In group A (SCS) patients, the cumulative risk was 8% at 1 year, 31% at 2 years, and then remained stable up to 5 years. In group B patients, the risk was low in the first 2 years and increased afterward: 2.5% at 1 year, 2.5% at 2 years, 8% at 3 years, 16% at 4 years, and 33% at 5 years. As in group A, the risk increased in the eleven cases with normal adrenal function (group C) only in the first 2 years after diagnosis (18% after 1 year, and 41% after 2 years) and thereafter remained stable. It is worth noting that one female subject exhibited a conspicuous tumor growth (from 1.5 to 4 cm) 6 months after the first presentation resulting from a malignant lesion, diagnosed after surgery as a diffuse large B-cell non-Hodgkin's lymphoma.

Risk of mass enlargement was significantly lower in subjects with subtle abnormalities (group B) than in patients with normal adrenal function (group C) (P = 0.03). Risk differences between subjects with SCS and subjects with mild endocrine abnormalities were not statistically significant (P = 0.35), possibly...
because of the small number of subjects included in the analysis.

During follow-up, nine patients underwent adrenal-

tomy. Seven of them, with a median follow-up of 30
months and including two subjects with SCS, had
shown a substantial mass enlargement (mean tumor
diameter from 2.7±0.4 to 4.2±0.1 cm). Surgery was
performed in the remaining two cases (mean tumor
diameter = 3.5 cm) and also taking the patients’
considerations into account. Histopathological examin-
ation revealed adrenocortical adenoma in six cases,
myelolipoma, leiomyoma, and B-cell non-Hodgkin’s
lymphoma in the three remaining subjects.

Discussion

In the present study, we evaluated the risk of endocrine
morbidty during follow-up of patients with an adrenal
 incidentaloma. Newly diagnosed subtle endocrine
alterations appeared in 28% of the patients, most of
them featuring a decrease in DHEA-S and ACTH
levels, as previously reported (14, 15). Similar small
changes in hormonal function have been reported by
Barzon et al. (14) and Grossrubatscher et al. (15).
Diagnosis of SCS was confirmed during follow-up, as
endocrine abnormalities tended to become more
evident. In fact, this condition encompasses a continu-
suum of abnormalities, ranging from mild
functional alterations in the hypothalamic–pituitary–
adrenal axis towards the appearance of overt adrenal
Cushing’s syndrome (14, 16). However, in our retro-
spective study no patient showed an evolution to
overt clinical hypercortisolism, in agreement with
previous reports (11, 15). When the initial mass size
was considered as a risk factor for adrenal hyper-
function, patients with a mass diameter ≥3 cm
showed a higher cumulative risk of developing hormo-
nal abnormalities than those with smaller lesions. The
risk was confined to the first 2 years of follow-up, indi-
cating the need for hormonal evaluation during this
time-period.

The second issue addressed in the present study con-
cerned the risk of mass enlargement. Most patients did
not show any change in mass size during follow-up. We
found an enlargement ≥1 cm in 20% of the cases, simi-
lar to two previous investigations (14, 15) that reported
an increase in tumor size in 17% and 15% of patients
respectively. No mass enlargement was observed in
two other small studies (17, 18) while, in larger
series, tumor growth was detected in a very low per-
centage of cases (3.3–4.3%) (19, 20). However, in
one of these studies (20), the investigators obtained
only indirect data from office records, or by telephone
or mail contacts for most patients. Previous studies
have documented occasional reduction or dis-
appearance of the adrenal lesions (14, 15), a finding
not confirmed in the present study.

We observed tumor growth in patients with subcli-
cial hypercortisolism, as well as in those with minor
endocrine abnormalities. In the former group, however,
tumor growth occurred early after diagnosis and was
slightly more frequent than in the latter. The possible
role in tumor growth of a higher intra-adrenal steroid-
ogenic activity, driven by ACTH or other factors,
remains to be elucidated. A similar cumulative risk of
mass increase in subjects with subtle endocrine
abnormalities was also reported by Barzon et al. (14),
while Grossrubatscher et al. (15) did not find any dif-
gence in mass enlargement between patients with or
without 17-OHP hyper-response to ACTH stimulation.
Some patients with normal hormonal function also
showed mass enlargement and, in this respect, the
possible risk of malignant transformation must always
be considered. Many studies have suggested that the
likelihood of malignant transformation at long-term
follow-up is very small (14, 17, 19, 20). We observed
a conspicuous mass increase in one woman 6 months
after diagnosis: adrenalectomy was performed to
remove the lesion, which was identified as a primary
non-Hodgkin’s lymphoma. In recent years, the exist-
ence of this rare disease has been increasingly reported
to advanced diagnostic imaging techniques
(21).

On the whole, these data indicate that conservative
management may be appropriate in most patients
with adrenal incidentalomas, since mass size did not
change in 80% of the cases. However, a prolonged
follow-up should be recommended, independently of
the mass size and the hormonal pattern at first presen-
tation. CT scans, although a close correlation with US
results was found, should be repeated every 6 months
for at least 2 years and then yearly, in order to either
detect malignant transformation or indicate, when
the mass diameter becomes larger than 4 cm, the
necessity of adrenalectomy, as occurred in seven of
our patients.

In conclusion, the present results suggest that
long-term follow-up of adrenal incidentaloma is recom-
dended, given the possibility of progressive tumor
growth or the evolution to hormonal hypersecretion.
Although the risk of malignant transformation is very
low, careful management with morphological evalu-
ation and hormonal determination is appropriate.

Acknowledgements

We thank Antonia Maffini for her technical assistance.

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Received 17 December 2001
Accepted 4 June 2002

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