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Adrenal incidentalomas showing unilateral concordant visualization by adrenocortical scintigraphy: Comparison with adenomas in Cushing's syndrome

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An adrenocortical adenoma causing Cushing's syndrome (Cushing's adenoma) produces a unilateral concordant visualization (UCV) imaging pattern in which the adenoma is only visualized on radioiodocholesterol adrenocortical scintigraphy. But because this imaging pattern is also noted in some patients with adrenal incidentalomas, we examined whether the UCV-incidentaloma was essentially identical with Cushing's adenoma and would develop Cushing's syndrome. The subjects were 9 patients with UCV-incidentalomas (mean size, 30 mm; range, 20–45 mm) and 6 patients with Cushing's adenomas (mean size, 28 mm; range, 25–35 mm). Endocrinological evaluations showed several abnormalities including blunted diurnal rhythm of plasma cortisol within the normal range, low plasma ACTH and/or high 24-hr urinary 17-OHCS levels in 8 of 9 patients with UCV-incidentalomas, but these abnormalities did not meet the diagnostic criteria of Cushing's syndrome. Adrenal uptake of the tracer in the patients with UCV-incidentalomas was not statistically different from that in the patients with Cushing's adenomas and had no relationship with hormonal values in either patient group. Tumor size on CT correlated with the levels of 24-hr urinary 17-OHCS ($r = 0.75$, $p = 0.02$) and plasma cortisol at 7 : 00 ($r = 0.82$, $p = 0.007$) in the patients with UCV-incidentalomas, but not in the patients with Cushing's adenomas. Although 3 UCV-incidentalomas increased slightly in size, none of 9 patients with UCV-incidentalomas has developed Cushing's syndrome for 4 to 52 months. These results suggest that the UCV-incidentaloma may be essentially different from the Cushing's adenoma and unlikely to develop Cushing's syndrome.

Key words: adrenal gland, incidentaloma, Cushing's syndrome, radioiodocholesterol

INTRODUCTION

INCIDENTALLY DISCOVERED ADRENAL MASSES (incidentalomas) have become a common clinical problem as a result of the wider application of high resolution anatomical imaging procedures, including computed tomography (CT), ultrasonography and magnetic resonance imaging.[1]

Adrenocortical scintigraphy has been reported to be useful in the evaluation of adrenal incidentalomas.[1–3] Increased uptake of the tracer in the tumor regardless of visualization of the contralateral gland suggests that the adrenal mass is functioning and is usually a benign adenoma.[1]

Increased uptake by the adrenal tumor and lack of uptake by the contralateral gland (unilateral concordant visualization) is characteristic of Cushing's syndrome caused by an adrenal adenoma, but it is not an unusual finding in incidentalomas.[1–8] Although endocrinological evaluation in patients with incidentalomas showing increased uptake of the tracer has been reported,[2,4–12] relationships of endocrine functions to radioiodocholesterol uptake in the tumor or tumor size were rarely reported.[13] In order to examine whether the incidentaloma showing unilateral concordant visualization (UCV-incidentaloma) is essentially identical with the adenoma in Cushing's

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Table 1 Patients characteristics

No.	Sex	Age (yr)	Clinical diagnosis	Location	Size (mm)	HT*	Follow-up period† (months)
1	F	44	UCV-incidentaloma‡	R	20	+	39
2	F	54	UCV-incidentaloma	L	25	+	28
3	M	46	UCV-incidentaloma	R	45	+	6
4	F	54	UCV-incidentaloma	R	25	-	52
5	M	72	UCV-incidentaloma	R	44	-	25
6	F	57	UCV-incidentaloma	R	20	+	14
7	F	46	UCV-incidentaloma	R	39	-	11
8	F	65	UCV-incidentaloma	R	23	+	18
9	M	67	UCV-incidentaloma	L	30	-	4
10	F	46	Cushing's syndrome	L	25	+	
11	M	43	Cushing's syndrome	L	35	+	
12	F	41	Cushing's syndrome	L	25	+	
13	F	42	Cushing's syndrome	L	25	+	
14	F	42	Cushing's syndrome	R	25	+	
15	F	66	Cushing's syndrome	L	30	+	

* Hypertension (more than 150/90 mmHg). † For patients with incidentalomas. ‡ Incidentaloma showing unilateral concordant visualization.

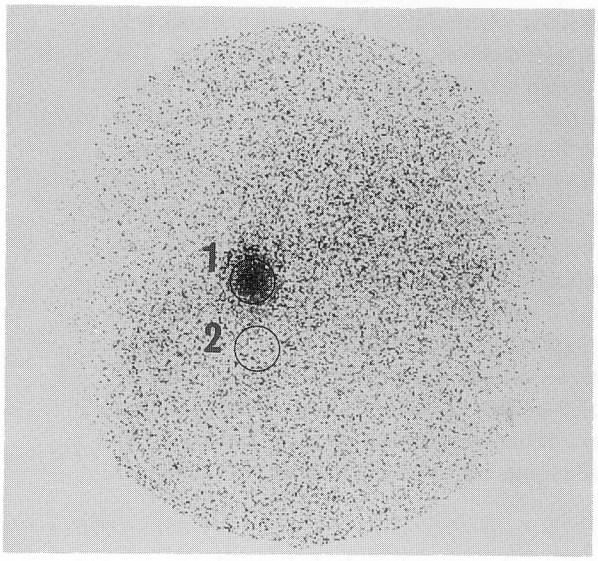

Fig. 1 An example of ROIs over the adrenal area (1) and background (2) on adrenocortical scintigraphy.

syndrome (Cushing's adenoma) and will develop Cushing's syndrome in future, we compared hormonal values and adrenal radioiodocholesterol uptake of patients with UCV-incidentalomas with those of patients with Cushing's adenomas, and assessed the relationships of hormonal values with the adrenal uptake and tumor size on CT in both patient groups.

MATERIALS AND METHODS

During the period between April 1994 and August 1999, 278 patients underwent adrenocortical scintigraphy at our institution. Of these 15 patients showed unilateral concordant visualization and were included in this study. A diagnosis of UCV-incidentaloma was made in nine patients (3 males and 6 females: 44 to 72 yr). All patients with UCV-incidentalomas were followed up for at least 4 months (4 to 52 months) with clinical examinations, measurements of plasma cortisol and adrenocorticotropic hormone (ACTH) and/or abdominal CT. The other six patients (one male and 5 females: 43 to 66 yr) had Cushing's syndrome caused by an adrenal adenoma which was confirmed by endocrinological examinations and surgery. All patients had abdominal CT at 2- or 5-mm collimation (Xvigor, Toshiba, Japan). Then the size of the adrenal mass was determined by the largest diameter of the lesion. The means for body-mass index were 23.8 and 22.1, respectively (normal range: 20 to 25). Hypertension (>150/90 mmHg) was observed in 5 of 9 patients with UCV-incidentalomas and all patients with Cushing's adenomas. Typical "moon face" was not observed in any patient with UCV-incidentaloma (Table 1).

Adrenocortical scintigraphy was performed 7 days after intravenous injection of 37 MBq of ^{131}I-6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (NCL-6-^{131}I) or NP-59.[14,15] The thyroidal uptake of free ^{131}I was blocked by daily oral administration of 300 mg potassium iodide from one day before to 6 days after intravenous injection of the tracer. Posterior imaging with data collection for 20 minutes was performed with a gamma camera (SNC-5100R, Shimadzu, Japan) equipped with a high-energy parallel-hole collimator. Regions of interest (ROIs) of the same size were drawn over the adrenal area and its caudal site to calculate the lesion-to-background ratios (Fig. 1). The mean counts per pixel of the adrenal ROI (Cmean), background ROI (Cb) and the maximum counts per pixel of the adrenal ROI (Cmax) were obtained in each patient. Then two types of lesion-to-background ratios were calculated as semiquantitative adrenal tumor uptakes; one was called the Rmean (Cmean/Cb) and the other was

Table 2 Results of endocrinological evaluation and scintigraphic parameters

No.	Cortisol* (μg/dL)		Aldosterone† (pg/mL)	ACTH‡ (pg/mL)	17-OHCS§ (mg/DAY)	17-KS¶ (mg/DAY)	Scintigraphic parameters	
	7 : 00	19 : 00					Rmean	Rmax
1	13.7	5.2	120	20.9	5.7	5.7	1.72	4.95
2	13.8	7.3	66	6.1	7.9	3.9	1.53	3.96
3	18.1	4.0	120	< 1.0	10.4	5.3	1.86	5.13
4	13.5	10.0	56	6.3	6.7	7.2	1.64	4.18
5	18.7	12.3	67	19.9	7.0	ND	1.75	4.61
6	13.0	7.0	110	18.8	4.0	1.7	1.29	3.19
7	13.3	5.5	100	17.2	7.7	3.7	2.36	5.85
8	13.0	7.7	75	3.0	4.5	3.9	1.98	4.60
9	15.1	7.3	60	< 1.0	6.1	5.4	1.90	4.80
10	25.6	26.7	10	< 1.0	24.7	6.8	1.82	4.85
11	25.8	22.1	17	< 1.0	18.2	8.4	1.97	5.39
12	23.1	30.8	61	< 1.0	14.1	6.7	2.33	5.67
13	24.8	24.0	48	< 1.0	12.0	4.0	2.01	4.17
14	28.6	ND	10	< 1.0	18.1	6.4	1.70	4.17
15	18.1	17.2	66	< 1.0	11.6	6.1	1.70	4.00

*Normal range = 5.0–20.0. †Normal range = 35.7–240. ‡ Normal range = 7.5–51.9.
§Normal range = 3.4–12.0 (M), 2.2–7.3 (F). ¶Normal range = 4.6–18.0 (M), 2.4–11.0 (F). __ = abnormal value.
ND = not done.

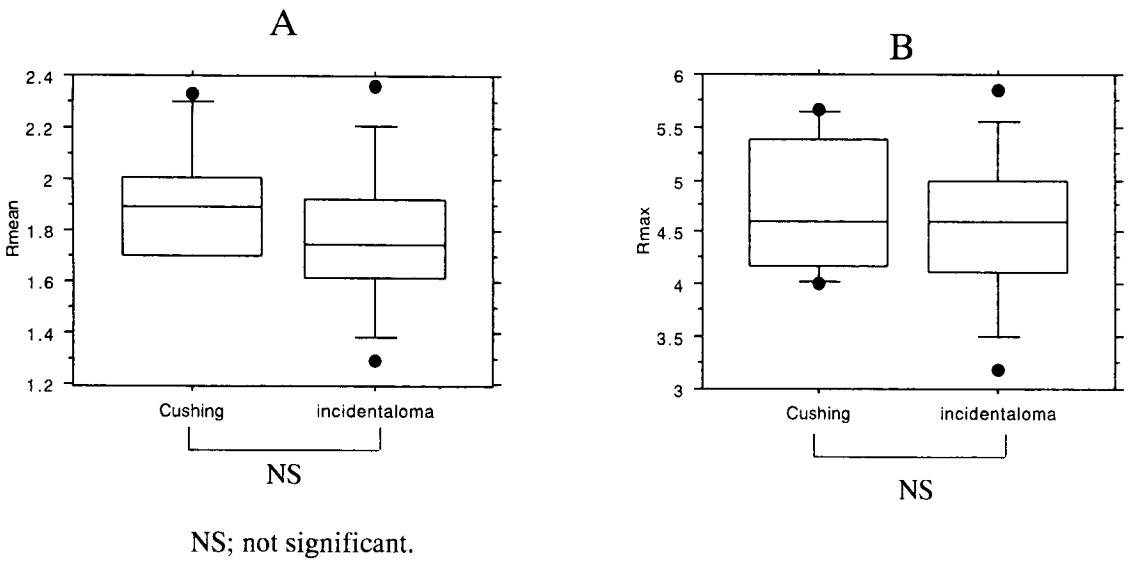

Fig. 2 Comparison of Rmean (A) and Rmax (B) between patients with Cushing's adenomas (Cushing) and patients with UCV-incidentalomas (incidentaloma). Although the median value of Rmean was higher in patients with Cushing's adenomas than in patients with UCV-incidentalomas, its difference was not statistically significant. The median value of Rmax was equal in each group.

called the Rmax (Cmax/Cb).

Endocrinological evaluation consisted of measurements of the levels of plasma cortisol, aldosterone, ACTH, 24-hr urinary 17-hydroxy-corticosteroids (17-OHCS) and 17-ketosteroids (17-KS). In all patients with UCV-incidentalomas, the level of plasma cortisol was measured at 7 : 00 and 19 : 00. The blunted diurnal rhythm of plasma cortisol was defined as the cortisol level at 19 : 00 greater than 60 percent but less than 75 percent of the cortisol level at 7 : 00.[5] The level of 24-hr urinary 17-KS was measured in all patients except one with a UCV-incidentaloma. The levels of plasma cortisol were determined by an enzyme immunoassay (AIA-PACK CORT, TOSOH Co., Japan). The levels of ACTH were assayed by an immunoradiometric assay (Allegro-ACTH kit, Nichols Institute Diagnostics—Nihon Medi-Physics, Japan). The levels of plasma aldosterone were measured by a radioimmunoassay, and those of urinary 17-OHCS and 17-KS were measured by colorimetry at SRL (Tokyo, Japan).

Table 3 Relationships of endocrinological values with tumor size, Rmean and Rmax

UCV-incidentaloma (n = 9)			Cushing's syndrome* (n = 5)		
Variables	r	p value	Variables	r	p value
Size			Size		
17-OHCS	0.75	0.02†	17-OHCS	−0.07	0.90
Cortisol (AM)	0.82	0.007†	Cortisol (AM)	−0.22	0.67
Cortisol (PM)	0.06	0.88	Cortisol (PM)	−0.61	0.28
Aldosterone	0.06	0.89	Aldosterone	−0.06	0.92
ACTH	0.31	0.49			
17-KS	0.15	0.72	17-KS	0.62	0.19
Rmean			Rmean		
17-OHCS	0.31	0.42	17-OHCS	−0.24	0.65
Cortisol (AM)	0.06	0.87	Cortisol (AM)	−0.22	0.97
Cortisol (PM)	−0.24	0.53	Cortisol (PM)	0.80	0.10
Aldosterone	0.02	0.95	Aldosterone	0.39	0.44
ACTH	−0.03	0.96			
17-KS	0.18	0.68	17-KS	0.02	0.97
Rmax			Rmax		
17-OHCS	0.50	0.17	17-OHCS	0.32	0.54
Cortisol (AM)	0.25	0.52	Cortisol (AM)	0.23	0.67
Cortisol (PM)	−0.35	0.35	Cortisol (PM)	0.70	0.19
Aldosterone	0.21	0.59	Aldosterone	−0.13	0.81
ACTH	0.19	0.68			
17-KS	0.34	0.40	17-KS	0.67	0.15

* Relationships including plasma ACTH were not evaluated because the levels of plasma ACTH were completely suppressed in patients with Cushing's syndrome. † Significant p value.

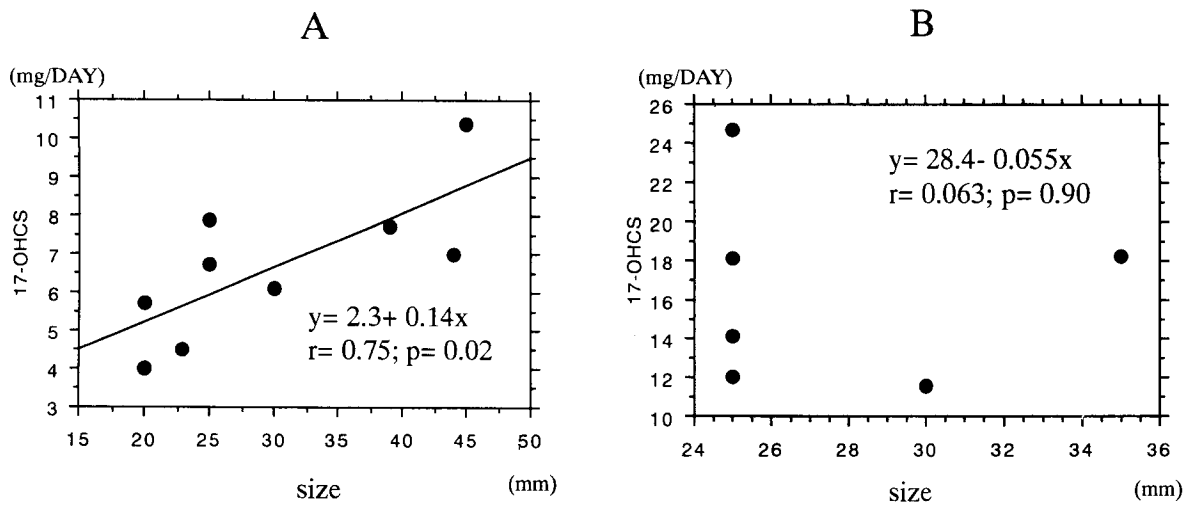

Fig. 3 Relationships between 24-hr urinary 17-OHCS levels and tumor size in patients with UCV-incidentalomas (A) and in patients with Cushing's adenomas (B). A significant correlation was observed in patients with UCV-incidentalomas.

To examine the relationships of endocrine functions to scintigraphic and radiologic parameters, hormonal values were correlated with the Rmean, Rmax and the tumor size on CT by linear regression analysis. Statistical analysis was conducted by the Mann-Whiteney U test. Levels of statistical significance were set at $p < 0.05$.

RESULTS

Table 2 shows the results of endocrinological evaluation and scintigraphic parameters. Endocrinological evaluations in the patients with UCV-incidentalomas showed a low plasma ACTH level alone in 3 patients (Nos. 3, 8, 9), a low plasma ACTH level with a high 24-hr urinary 17-OHCS level in one patient (No. 2), a low plasma ACTH

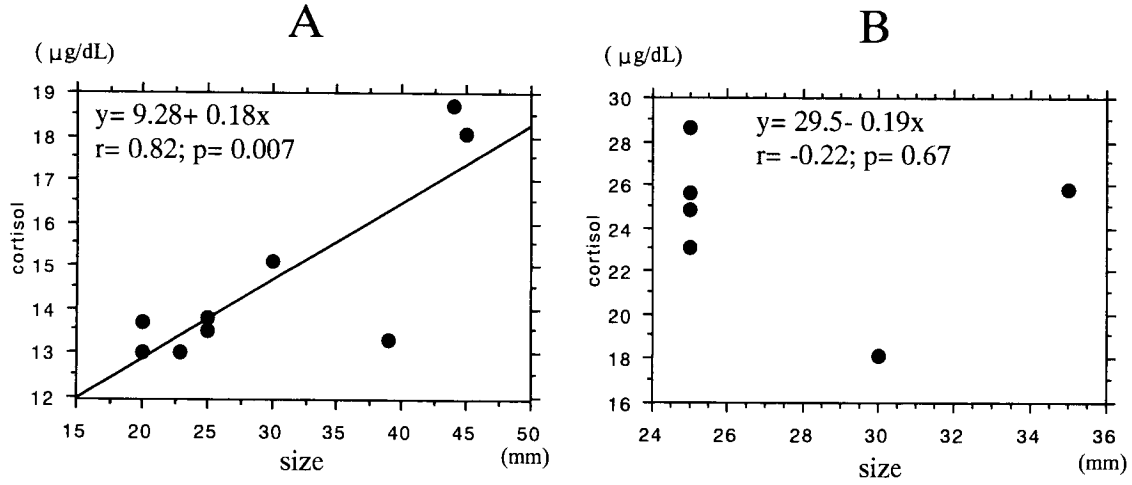

Fig. 4 Relationships between plasma cortisol levels and tumor size in patients with UCV-incidentalomas (A) and in patients with Cushing's adenomas (B). A significant correlation was observed in patients with UCV-incidentalomas.

Table 4 Follow-up hormonal values and tumor size in patients with UCV-incidentalomas

No.	Follow-up period (months)	Cortisol (μg/dL)	ACTH (pg/mL)	Size (mm)	Increase in diameter (mm)
1	39	8.8	20.2	25	+5
2	28	16.1	2.2	27	+2*
3	6	19.6	< 1.0	45	0
4	52	17.0	11.2	25	0
5	25	13.4	9.5	47	+3†
6	14	9.4	14.7	20	0
7	11	7.7	3.7	39	0
8	18	10.3	ND	23	0
9	4	11.2	4.3	30	0

ND = not done. __ = abnomal value. * Follow-up CT was performed at 16 months.
† Follow-up CT was performed at 19 months.

level with blunted diurnal rhythm of plasma cortisol in one patient (No. 4), a blunted diurnal rhythm of plasma cortisol alone in one patient (No. 5), a low 24-hr urinary 17-KS level alone in one patient (No. 6), a high 24-hr urinary 17-OHCS level alone in one patient (No. 7), and normal values in one patient (No. 1). The levels of plasma cortisol and aldosterone at 7 : 00 were within the normal range in all patients with UCV-incidentalomas. In the patients with Cushing's adenomas, endocrinological evaluation revealed high plasma cortisol levels without a diurnal rhythm, suppressed plasma ACTH levels and high 24-hr urinary 17-OHCS levels. These findings were adequate for the diagnosis of Cushing's syndrome.

The median Rmean and Rmax values in the patients with UCV-incidentalomas were 1.86 (range: 1.29 to 2.36) and 4.61 (range: 3.19 to 5.85), respectively. In the patients with Cushing's adenomas, these values were 1.90 (range: 1.70 to 2.33) and 4.61 (range: 4.00 to 5.67). There was no significant difference between the two groups in these ratios (Fig. 2).

Table 3 shows the relationships of endocrinological values to tumor size, Rmean and Rmax. The size of the adrenal masses was significantly correlated with the levels of 24-hr urinary 17-OHCS and plasma cortisol in the patients with UCV-incidentalomas ($r = 0.75$, $p = 0.02$; $r = 0.82$, $p = 0.007$) (Figs. 3, 4). But Rmean and Rmax were not significantly correlated with the levels of any hormonal values. In the patients with Cushing's adenomas, neither scintigraphic parameters nor tumor size were correlated with the endocrinological values.

Table 4 shows the follow-up hormonal values and tumor size on CT in the patients with UCV-incidentalomas. During the follow-up periods, an increase in tumor size was observed in 3 patients (No. 1, 5 mm for 39 months; No. 2, 2 mm for 16 months; No. 5, 3 mm for 19 months). None of the patients with UCV-incidentalomas showed signs of clinical or endocrinological progression to overt hypercortisolism for 4 to 52 months.

DISCUSSION

Unilateral concordant visualization on adrenocortical scintigraphy is not an unusual finding in patients with incidentalomas,[1,3,7] but its incidence is unknown. Nakajo et al. reported that 2 patients with unilateral concordant visualization were noted among 12 patients with incidentally discovered adrenal adenomas.[3] Barzon et al. reported that unilateral concordant visualization was observed in 37 of 91 patients with incidentalomas who showed increased ^{75}Se-Methylcholesterol uptake by the tumors.[7]

In Cushing's syndrome, the pattern of unilateral concordant visualization is the result of uptake of radioiodocholesterol by a cortisol-hypersecreting adenoma with suppression of ACTH and radioiodocholesterol uptake in the contralateral adrenal gland.[16] But patients with UCV-incidentalomas have few symptoms and endocrinological evidence of typical Cushing's syndrome. Therefore the entity termed pre-Cushing's syndrome, subclinical Cushing's syndrome or preclinical Cushing's syndrome has been introduced,[4,5,17] but these terms anticipate the development of Cushing's syndrome in future. Although Barzon et al. reported that two of eleven patients with nonclinical "hypercortisolism" and scintigraphic evidence of unilateral concordant visualization developed overt Cushing's syndrome without changes in tumor size,[7] it is not known whether such silent adenomas without overt hypersecretion of cortisol, as ours, progress toward clinical and biological Cushing's syndrome.

In the present study, we compared the patients with UCV-incidentalomas and Cushing's adenomas as to endocrine functions, NCL-6-^{131}I uptake by the tumor, the relationship of endocrine functions to adrenal tumor uptake and tumor size in order to study this problem.

Most of our patients with UCV-incidentalomas had various endocrinological abnormalities, a blunted diurnal rhythm of plasma cortisol, low plasma ACTH levels, high 24-hr urinary 17-OHCS levels and a low 24-hr urinary 17-KS level, but none of the endocrinological findings in each patient fulfilled the criteria of Cushing's syndrome. The reported endocrinological abnormalities in patients with UCV-incidentalomas include increased urinary free cortisol,[7,8,10,12] blunted suppressibility of plasma cortisol after dexamethasone administration,[7–12] decreased plasma dehydroepiandrosterone sulfate[9,11,12] and blunted diurnal rhythm of cortisol secretion.[7,9,11,12,18] These abnormalities are similar to our results and suggest autonomous cortisol secretion by the incidentaloma at a rate insufficient to give clinical expression, but able to inhibit to some degree the hypothalamic-pituitary-adrenal axis.

In our study, the concentration of radioiodocholesterol in the adrenal tumor was similar in the UCV-incidentalomas and the Cushing's adenomas and no correlation was observed between endocrinological data and adrenal intensity. This could be explained as follows[16]: Cholesterol is the biosynthetic precursor for all steroid hormones; and the radioiodocholesterols, as a result of their structural similarity to cholesterol, are accumulated within the adrenal cortex by the same mechanism as plasma cholesterol. Plasma cholesterols transfer to the adrenal cortical cells after binding to lipoproteins. Once inside the adrenal cell, cholesterol is stored as cholesterol esters and used for steroid hormone biosynthesis, but the radioiodocholesterols appear not to be used for steroid biosynthesis, and appear to be stored in the cholesterol ester storage pool. Therefore it is cholesterol uptake, and not steroid production, that is necessary for concentration of radioiodocholesterol by the adrenal.[19] Our results suggest that cholesterol uptake by incidentalomas may not be different from that by Cushing's adenomas.

Then, from where are the cholesterols for overproduction of cortisol in Cushing's adenoma derived? Another possible route of cholesterol for steroidogenesis is de novo synthesis of cholesterol from acetate in the adrenal adenoma cells. A previous study demonstrated that, at rest, about 80% of the hydrocortisone is derived from plasma cholesterol, the other 20% being synthesized *in situ* from acetate and other precursors in human adrenals.[20] Therefore, the cholesterols for overproduction of cortisol in Cushing's adenomas may be derived from the de novo synthesis.

In our study, adrenal intensity did not correlate with the endocrinological data in the patients with Cushing's adenomas. This agrees with a previous report that, in ACTH-independent Cushing's syndrome, no relationship was seen between NP-59 uptake and urinary free cortisol, or between NP-59 uptake and urinary 17-OHCS, 17-KS, the cortisol secretion rate, plasma cortisol and ACTH levels, although a significant positive correlation was observed between 24-hr urinary free cortisol excretion and NP-59 adrenal gland uptake in the patients with ACTH-dependent Cushing's syndrome.[21]

In patients with UCV-incidentalomas, the relationship of endocrine function to tumor size has rarely been studied. Tsagarakis et al. reported that cortisol values after low-dose dexamethasone suppression test correlated positively with the size of the adrenocortical adenoma.[13] In the present study, the levels of 24-hr urinary 17-OHCS and plasma cortisol at 7 : 00 significantly correlated with the size of adrenal masses in the patients with UCV-incidentalomas but not with Cushing's adenomas. This suggests that the amount of cortisol produced is dependent on tumor volume in UCV-incidentalomas but not in Cushing's adenomas. As shown in Figures 3 and 4, Cushing's adenomas produced 2–3 times as much cortisol and 17-OHCS as the same 25-mm sized UCV-incidentaloma. This suggests a difference between Cushing's adenomas and UCV-incidentalomas in the nature of the cells producing hormones. If the UCV-incidentaloma develops Cushing's syndrome, the tumor

should grow to more than 7 cm in diameter, which is calculated from the equations, y (the level of 17-OHCS) = $2.3 + 0.14x$ (tumor size in mm) and y (the level of cortisol) = $9.28 + 0.18x$ (tumor size in mm), assuming that the level is 12 mg/day for urinary 17-OHCS and 23.1 $\mu g/dl$ for plasma cortisol (these were the lowest values in the patients with 25 mm Cushing's adenomas in our study). A previous study revealed that the adenoma of Cushing's syndrome was 3.3 ± 1.0 cm (range: 2.0 to 5.0) in diameter and the mean age at diagnosis was 39.6 ± 14.4 years (n = 27),[22] and in our 6 patients with Cushing's adenomas (age range: 41 to 66), the tumors also ranged between 2.5 and 3.5 cm in diameter. Three (Patients Nos. 1, 2 and 5) of 9 UCV-incidentalomas increased slightly in size during the follow-up periods (16–39 months) in this study. They were 44, 54 and 72 years old respectively, at the time of diagnosis. If these tumors should increase at the same rate as those during the individual follow-up periods, they will take 32.5 years, 30 years and 13.7 years to grow to 7 cm in diameter, which might produce sufficient amount of cortisol to develop Cushing's syndrome and they would be 76.5, 84 and 85.7 years old respectively at the time. But we could not find cases of Cushing's syndrome due to such a large "adenoma" (not carcinoma) developed in such elderly patients. In addition, Barry et al.[23] reported that an adrenal incidentaloma demonstrating an increase in size > 1 cm was observed in only 4 of 91 (4.4%) patients during the follow-up period (mean: 7 years; range: 1 months to 11.7 years): One was a hemorrhagic cyst and the other three were adenomas which increased in size 12–35 mm in between 6 and 35 months. However, these three patients were still asymptomatic at the time of surgery. Therefore the UCV-incidentaloma is unlikely to develop Cushing's syndrome.

In conclusion, an adrenal incidentaloma showing scintigraphic and endocrinological evidence of autonomous and normal ranged cortisol secretion may be essentially different from an adenoma producing Cushing's syndrome and unlikely to develop Cushing's syndrome.

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