CASE REPORTS

Does the Corticoadrenal Adenoma with "Pre-Cushing's Syndrome" Exist?

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An adrenal tumor was discovered fortuitously in a patient with no clinical features of Cushing's syndrome. On adrenal imaging, there was good uptake in the nodule but no visualization of the contralateral adrenal. The latter was seen, however, in a second scan performed under ACTH treatment. In the hormone assessment, basal cortisol and 17-hydroxycorticoids were normal and cortisol diurnal variation was near normal, but a dexamethasone suppression test and ACTH responses to metyrapone and insulin hypoglycemia were abnormal. Eight months after excision of a spongiocytic-type adenoma, the remaining adrenal was visible on scintigram and the hormonal tests were normal. This pattern suggests that the tumor produced autonomously small amounts of cortisol, insufficient to provide a clinical Cushing's syndrome but enough to suppress partially ACTH and, consequently, visualization of the contralateral gland.

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In 1974, Beierwaltes et al. (*1*) reported two cases of functional adrenal nodules presenting the scintigraphic profile of Cushing's adenoma (*2*) but not associated with clinical Cushing's syndrome. In 1978, Rizza et al. (*3*) reported four similar cases and proposed that the lipid content of adrenal tissue could of itself account for the scintigraphic picture without any assumed secreting nodules.

We present such a case, including a complete corticotropic assessment before and after surgery. It confirms the existence of functional pre-Cushing corticoadrenal adenomas.

CASE REPORT

The subject, a 50-yr-old man in good health, presented with epididymitis in 1974. Intravenous urography revealed a right suprarenal nodule. There was not the slightest clinical sign of Cushing's syndrome.

The patient refused all further investigation until January 1978, at which time selenonorcholestenol (Se-75)* adrenal imaging was performed according to a previously published protocol (*4*). There was good uptake 6 days after tracer administration (day + 6) in the nodule on the right, but the left adrenal did not show up (Fig. 1). A second adrenal scintigram, using 19-iodocholesterol (I-131),† was performed in August 1978 under i.m. administration of depot-tetracosactrin, 0.50 mg/day from day −6 to day +6. Once again there was good uptake in the tumor at day +6, and this time a normal left adrenal appeared ("scintigraphic reactivation," Fig. 2). Transmission computerized tomography (Fig. 3) and ultrasound confirmed the existence of the nodule.

In March 1979 the subject agreed to surgery. The clinical examination remained normal, with no sign of Cushing's syndrome 5 yr after the first discovery of the nodule. Weight and blood pressure were normal. The usual biological and hormonal data were normal, including catecholamines, vanillylmandelic acid, metanephrines, aldosterone, 17-ketosteroids, DHEA, and D_4 androstene-dione.

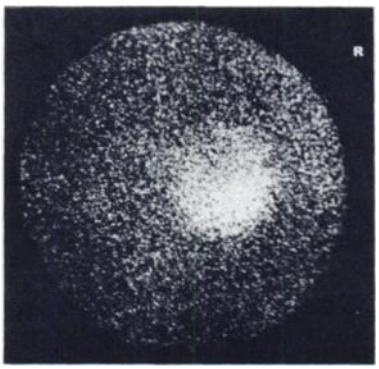

FIG. 1. Preoperative posterior adrenal scintigram at 6 days after selenonorcholestenol (Se-75). Tumor shows good uptake, with none in left adrenal.

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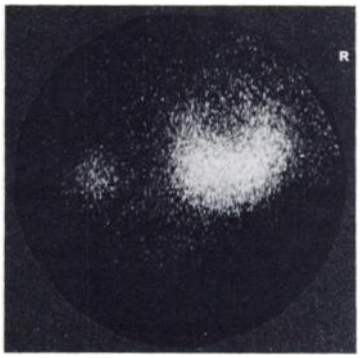

FIG. 2. After 11 days of ACTH, preoperative posterior adrenal scintigram at 6 days after 19-iodocholesterol(I-131). Here is "scintigraphic reactivation" of normal left adrenal.

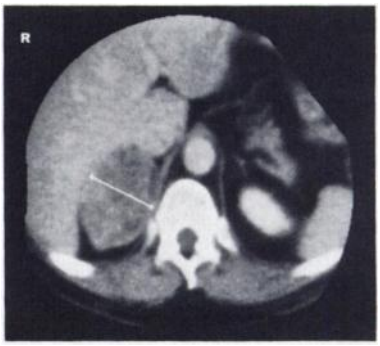

FIG. 3. TCT scan of right adrenal tumor.

The laboratory data showed a preserved circadian rhythm for cortisol, although the depressions at 8 p.m. and midnight were unimpressive. Urinary 17-hydroxycorticoids were normal (6 mg/24 hr); plasma ACTH was consistently undetectable at 8 a.m. The dexamethasone test was not normal (Table 1): urinary 17-hydroxycorticoids did not decrease and the plasma cortisol drop (at the midnight spontaneous level) was insufficient. Corticotropic stimulation tests were also abnormal (Table 1): metyrapone gave no ACTH response and an inadequate rise of 17-hydroxycorticoids and plasma S-compounds; the response to insulin-induced hypoglycemia was normal for cortisol but inadequate for ACTH.

On March 22, 1979, an operation easily removed a right adrenal nodule of weight 165 g and measuring 7.5 × 6 × 5 cm. Before adrenalectomy the cortisol level in the tumor's efferent vein was elevated (>60 μg/dl), whereas it was normal in the peripheral blood (15 μg/dl). Microscopy revealed proliferation of spongiocytic-type cells with no malignant changes, a picture judged typical of adrenocortical adenoma. The adrenal parenchyma appeared atrophied around the periphery.

Eight months after the operation, a complete adrenal examination was performed. The clinical state was good. A control scan of the adrenal area ruled out residual activity from earlier tests, after which a selenonorcholestenol(Se-75) scintigram showed uptake in the left adrenal, the one previously blank except during ACTH stimulation. Abnormal hormone levels had returned to normal, the circadian rhythm of cortisol was normal (including midnight), and basal ACTH levels were consistently normal. Metyrapone and insulin-induced hypoglycemia gave clearly positive ACTH responses (Table 1).

The subject left the department without further treatment. As of December 1980 he remains in good health.

METHODS

Assays. Plasma cortisol and 11-deoxycortisol were measured by competitive protein binding after dichlometan extraction and partition between water and carbon tetrachloride (*5*). Plasma ACTH was measured by RIA, using an antiserum produced in the laboratory (*6*).

Dynamic hormonal tests. These were performed in the following order. Hypoglycemia: insulin i.v., 0.15 units/kg. Metyrapone: 750

TABLE 1. HORMONAL DYNAMIC TESTS

	Preoperative				Postoperative			
	Plasma cortisol 8 h μg/dl	Plasma ACTH pg/ml	Plasma 11-deoxycortisol 8 h μg/dl	Urinary 17 OH CS mg/24 h	Plasma cortisol 8 h μg/dl	Plasma ACTH pg/ml	Plasma 11-deoxycortisol 8 h μg/dl	Urinary 17 OH CS mg/24 h
Metyrapone								
Basal values	16	<10	—	6	8	77	<1	3.1
D 0	—	—	—	3	—	—	—	5.3
D 1	2	<10	6	8	2	155	5	12
Insulin-induced hypoglycemia *								
Basal 0	9	<10	—	—	9	73	—	—
+20′	10	<10	—	—	7	—	—	—
+40′	13	36	—	—	9	207	—	—
+60′	17	28	—	—	13	211	—	—
+80′	—	—	—	—	13	179	—	—
+90′	16	20	—	—	—	—	—	—
Dexamethasone								
D 3	5	<10	—	6.2	—	—	—	—
D 5	7	<10	—	6.8	—	—	—	—

* Blood glucose lowered to 1.38 mmol/l and 1 mmol/l.

mg p.o. every 4 hr for 24 hr, starting at 1000 hr. Dexamethasone: 0.5 mg every 6 hr for 5 days.

DISCUSSION

This case confirms the existence of "pre-Cushing's" adrenocortical adenomas presenting a clinical, hormonal, and scintigraphic profile analogous to that of pretoxic functional adenomas of the thyroid.

The nodule was detected fortuitously in a patient with no clinical signs of Cushing's syndrome. Although 5 yr passed between the discovery of the tumor and its surgical excision, the absence of clinical hyperadrenocorticism conformed with the basal hormone assessment, which was close to normal. However, dynamic hormone tests showed mild but indisputable disturbances. Everything suggested that the nodule was autonomously producing small amounts of cortisol, which allowed the corticotropic system only a limited range of regulation. The cortisol level never dropped below 5 to 7 μg/dl, whether spontaneously at midnight or under dexamethasone. This places autonomous secretion by the nodule at this level. The result was a corticotrophin suppression: basal plasma ACTH could never be measured. It may also be unmeasurable in 25% of normal subjects, but our patient's ACTH response to the dynamic tests was negative or insufficient. Conversely, after the operation, plasma cortisol dropped normally at midnight, and there was a normalization of basal plasma ACTH and the responses to metyrapone and hypoglycemia.

The case presented here is similar to the two cases reported by Beierwaltes et al. (*1*) and to the four cases reported by Rizza et al. (*3*), but it is the first to include a complete hormone assessment before and after surgery. The scintigraphic image is thus not to be explained exclusively by the lipid content of tumoral adrenal tissue, as suggested by Rizza et al., but clearly results, as Beierwaltes suggests, from the uptake of the tracer in a nodule autonomously producing small amounts of cortisol. These are sufficient to suppress ACTH and, consequently, uptake in the healthy adrenal, but are not sufficient to provide clinical signs of Cushing's syndrome. The "scintigraphic reactivation" of the contralateral adrenal by exogenous ACTH before surgery, and its spontaneous uptake after surgery, confirm this point of view.

It is difficult to be certain about the future course of such "pre-Cushing's" corticoadrenal adenomas. Are all Cushing's adenomas preceded by this situation for a while? Does the syndrome necessarily evolve toward a clinical and biological hyperadrenocorticism? Our case is interesting in that 5 yr passed between the discovery of the nodule and its surgical excision, with no change in either the nodule's dimensions or the clinical picture. The frequency of these corticoadrenal adenomas associated with "pre-Cushing's syndrome" is also difficult to estimate. It is possible that a certain number of adrenal nodules labeled as nonfunctioning before the use of adrenal scintigraphy actually belonged in this syndrome, so it seems desirable to perform a scan in the case of every adrenal nodule, even an apparently nonsecreting one, because of the influence of this diagnosis on the therapeutic precautions to be taken at the time of surgery.

FOOTNOTES

* Scintadren. The Radiochemical Center, Amersham, England.
† CHOL-131, CIS; Gif-sur-Yvette, France.

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