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# A Pituitary Adenoma Secreting High Molecular Weight Adrenocorticotropin without Evidence of Cushing's Disease

M. REINCKE, B. ALLOLIO, W. SAEGER, D. KAULEN, AND W. WINKELMANN

*Medizinische Universitätsklinik II, Köln-Merheim, Köln; and Abteilung für Pathologie (W.S.), Marienkrankenhaus Hamburg, Hamburg, West Germany*

**ABSTRACT.** We report a patient with hypersecretion of a high mol wt ACTH from an aggressive corticotropic pituitary tumor who did not have hypercortisolism. Basal plasma ACTH levels were clearly elevated (26–121 pmol/L), whereas basal and stimulated serum cortisol levels were in the normal range. The pituitary source of the ACTH hypersecretion was confirmed by selective venous catheterization. Gel chromatography of the patient's plasma showed two peaks of ACTH immunoreactivity, one major peak eluting near the void volume (high mol wt form of ACTH), accounting for more than 95% of the ACTH detected, and a very small peak at the expected position of ACTH-(1–39).

Plasma ACTH levels were not altered by metyrapone or bromocriptine. During high dose dexamethasone administration plasma ACTH decreased, but was not fully suppressed. Immunohistochemical evaluation of tumor tissue demonstrated ACTH immunoreactivity in 40% of the tumor cells. The patient died from postoperative complications after a second operation performed after tumor recurrence. This patient's course confirms the observations of relatively rapid growth and high recurrence rate in clinically silent corticotropic pituitary adenomas. (*J Clin Endocrinol Metab* 65: 1296, 1987)

**A**MONG surgically removed pituitary adenomas, approximately 30–35% appear to be silent, unassociated with clinical or biochemical evidence of any anterior pituitary hormone excess (1, 2). However, with routine immunocytochemical staining of the pituitary tumor tissue, immunoreactive hormone material can be demonstrated in a substantial number of these seemingly nonfunctioning tumors (2). Clinically silent immunoreactive FSH- and LH-containing pituitary adenomas were reported by Trouillas *et al.* in 1981 (3). More recently, silent pituitary adenomas secreting  $\alpha$ -subunit have been described (4). Corticotropic pituitary adenomas without evidence of Cushing's disease have been reported by Hassoun *et al.* in 1979 (5) and in more detail by Horvath *et al.* in 1980 (2). However, secretion of biologically inactive ACTH in patients with silent corticotropic adenomas has not been described. We report here a patient with hypersecretion of immunoreactive ACTH from a clinically silent pituitary adenoma.

## Case Report

A 46-yr-old man was admitted to the Städtische Krankenanstalten Köln-Merheim in May 1981 with a 6-month history

of visual problems followed by decreased libido. The visual acuity in his left eye was diminished, but no temporal visual field defect was found. He was mildly obese (height 1.76 m; weight, 79 kg), but had no clinical features of hypercortisolism. Serum electrolytes were normal. Glucose tolerance (100 g glucose, orally) was abnormal, with a fasting blood glucose level of 5.0 mmol/L and a 2-h value of 13.6 mmol/L. Skull x-rays showed an enlarged pituitary fossa. Computerized axial tomography revealed an intrasellar tumor with suprasellar and parasellar extension. In July 1981 he underwent transfrontal craniotomy, but only incomplete removal of the tumor was achieved. Postoperative recovery was uneventful, and his visual acuity returned to normal. Tumor recurrence necessitated a second operation in March 1983. He died from pulmonary embolism soon after surgery. At autopsy no carcinoma, *i.e.* bronchial carcinoma, or metastases were found. The weight of the adrenal glands was normal.

## Materials and Methods

Assessment of hormonal status was performed before and after the first craniotomy. Plasma ACTH was measured in triplicate by RIA (6) after extraction with QUSO (7). The antibody cross-reacted completely with ACTH-(1–24), human (h) ACTH-(1–39), and ACTH-(11–24), and did not react with ACTH-(1–10), hACTH-(27–39),  $\beta$ hMSH, or  $\alpha$ hMSH. Plasma ACTH also was measured in duplicate by a highly specific two-site immunoradiometric assay for hACTH-(1–39). This antibody did not react with hACTH-(1–32), ACTH-(1–24), and hACTH-(18–39) (8). Plasma  $\beta$ -endorphin was determined by

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Address all correspondence and requests for reprints to: Dr. M. Reincke, Medizinische Universitätsklinik II, Köln-Merheim, Ostmerheimer Str. 200, 5000 Köln 41, West Germany.

RIA after extraction with Vycor powder (9). The antibody had 58% cross-reactivity with  $\beta$ -lipotropin. Synthetic  $\beta$ -endorphin (Universal Biologicals, Cambridge, United Kingdom) was used for standard and radioiodination. Urinary cortisol excretion was determined after extraction and chromatography (10). The serum levels of other hormones were measured by standard RIA techniques using commercially available reagents.

Analysis of the molecular size of the circulating immunoreactive ACTH was performed by gel chromatography, as described by Ratter *et al.* (11). Acidified plasma was chromatographed on a column of Sephadex G-75 (superfine;  $100 \times 1.5$  cm) equilibrated with 1% formic acid.

Sections of the tumor tissue were examined by light microscopy using conventional and immunocytochemical techniques, described previously (12). Using the peroxidase-antiperoxidase method on paraffin-embedded sections, the following commercial primary antibodies were tested: anti-ACTH [synthetic  $\beta$ ACTH-(1-23), Ferring Arzneimittel, Wittland, West Germany; dilution 1:200], anti-ACTH (synthetic ACTH-(1-24), Dakopatts, Hamburg, West Germany; 1:300), anti-CRH (Medac, Hamburg, West Germany; 1:20), anti-GH (Dakopatts; 1:500), anti-GH (Kabi vitrum, München, West Germany; 1:100), anti-PRL (Dakopatts; 1:800), anti-TSH (Kabi vitrum; München, West Germany 1:200), anti-FSH (Dakopatts; 1:200), and anti-LH (Dakopatts; 1:800). Normal adenohypophysis and hypothalamus were used as control tissues for immunocytochemistry. The three traditional types of control reactions, increase in dilution, omitting components, and antiserum preabsorption with antigen excess, were performed.

## Results

Preoperatively, thyroid function was normal. Gonadotropin secretion in response to stimulation with GnRH was diminished, and serum testosterone was in the low normal range. Baseline serum PRL and the PRL response to TRH were normal. Serum GH did not increase after insulin-induced hypoglycemia.

No signs of adrenal hyperfunction were found. The 24-h urinary cortisol excretion was 69 nmol/day (normal, 55–176 nmol/day). Baseline serum cortisol as well as the cortisol response to exogenous ACTH and insulin-induced hypoglycemia were normal preoperatively (Table 1). The serum cortisol values displayed a normal diurnal variation (0900 h, 440; 1000 h, 360; 1100 h, 310; 1200 h, 250; 1300 h, 220 nmol/L). Postoperatively, the response to insulin-induced hypoglycemia was impaired (peak serum cortisol, 330 nmol/L), whereas the cortisol response to exogenous ACTH remained normal.

In contrast, preoperative plasma radioimmunoassayable ACTH levels were clearly elevated (35–82 pmol/L at 0900 h; normal range, <11 pmol/L). One month after the first operation, plasma ACTH was 50 pmol/L at 0900 h. It remained elevated (26–131 pmol/L at 0900 h), suggesting the presence of a tumor secreting biologically inactive ACTH. Similarly, plasma  $\beta$ -endorphin immunoreactivity was increased (3220 ng/L; normal, <230).

While serum cortisol was readily suppressed by dexamethasone, plasma ACTH immunoreactivity was elevated throughout the test period, though it decreased from 131 to 50 pmol/L (Fig. 1). Thus, partial suppression of the secretion of biologically inactive ACTH together with complete suppression of biologically active ACTH, probably secreted by nontumorous cells, occurred. Plasma ACTH levels, measured at 0, 120, 180, 240, and 300 min, did not change after metyrapone (2.0 g, iv) or bromocriptine (2.5 mg, orally) administration, demonstrating autonomy of tumor peptide secretion, but increased after lysine vasopressin (Table 1).

Plasma ACTH measured by immunoradiometric assay (IRMA) was in the low normal range and increased slightly after lysine vasopressin administration (Table 1), suggesting release of biologically active ACTH in the presence of a tumor secreting biologically inactive ACTH.

To investigate the molecular size of the circulating biologically inactive ACTH, gel chromatography was performed. Gel chromatography of plasma of an Addisonian patient revealed a single peak of immunoreactive ACTH (Fig. 2a), eluting at the same position as [ $^{125}$ I]ACTH-(1-39). The patient's plasma, fractionated under the same conditions, showed two peaks (Fig. 2b). A very small peak appeared at the expected position of ACTH-(1-39); the second, predominant peak, eluting near the void volume, indicated the presence of a large mol wt form of ACTH. This peak accounted for more than 95% of the ACTH detected. In contrast, the plasma of a patient with an ACTH-secreting bronchial carcinoma and Cushing's syndrome had a heterogenous, large mol wt peak (Fig. 2c), indicating the release of a variety of peptides with different mol wt.

To exclude ectopic ACTH secretion, selective venous sampling was performed. This procedure confirmed a pituitary source of the ACTH hypersecretion (gradient from high internal jugular vein to inferior vena cava, 1.4 to 1).

Histologically an undifferentiated mucoid cell adenoma was found. Very few mitoses and cells with two or more nuclei were seen. Periodic acid-Schiff staining revealed a few strongly granulated cells and a large number of very slightly granulated cells. Immunohistochemical studies demonstrated ACTH immunoreactivity in 40% [anti-ACTH-(1-23); Fig. 3] or 15% [anti-ACTH-(1-24)] of the adenoma cells, whereas GH, PRL, and CRH were not detected. TSH and FSH were found in a few scattered cells. At autopsy, the adenoma invaded the capsule, the neurohypophysis, the sellar bone, and the sphenoid sinus. Little intact adenohypophyseal tissue was found, and it contained different cell types and very few immunoreactive ACTH-containing cells with partial hyalinization. Fully developed Crook's cells were not found.

TABLE 1. Preoperative serum cortisol and/or plasma ACTH (RIA and IRMA) responses at 0900 h to exogenous ACTH (250  $\mu$ g, iv), insulin-induced hypoglycemia (0.15 IU/kg), and lysine vasopressin administration (5 IU, iv, for 60 min)

Time (min)	Response to ACTH: cortisol (nmol/L)	Response to insulin-induced hypoglycemia: cortisol (nmol/L)	Response to lysine vasopressin:		
			ACTH (RIA; pmol/L)	ACTH (IRMA; pmol/L)	Cortisol (nmol/L)
0	350	410	96	5	290
15			143	6	500
30	960	480	114	6	790
45		940	118	7	820
60	1160	980	89	7	820
90	1250	880	83	6	550

Normal basal (0900 h) values: serum cortisol, 140–690 nmol/L; ACTH (RIA and IRMA), <11 pmol/L.

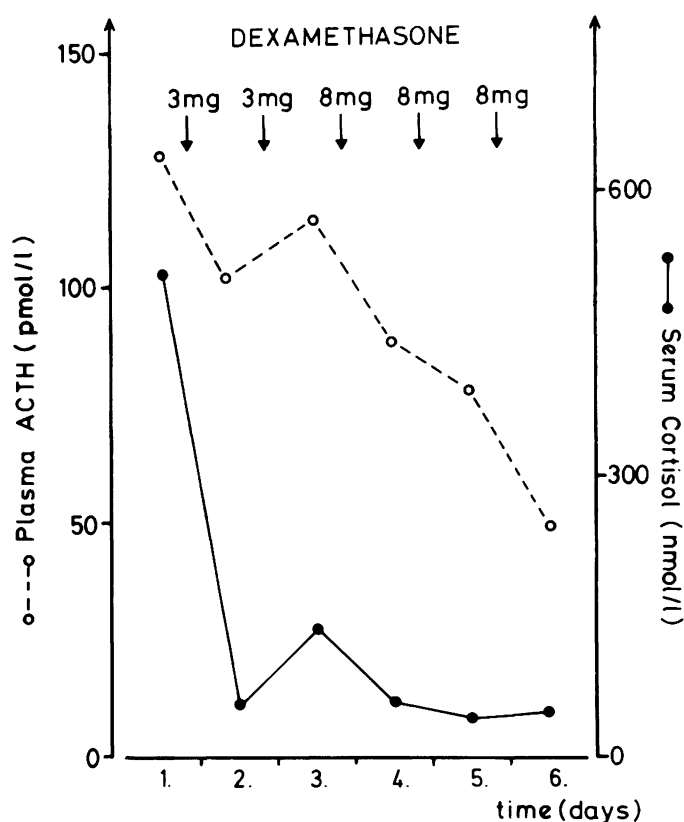


FIG. 1. Serum cortisol and plasma ACTH (RIA) concentrations during administration of dexamethasone.

### Discussion

The major finding in this patient was the secretion of a high mol wt form of ACTH by a pituitary adenoma in the absence of hypercortisolism. Clinically, the large pituitary tumor resulted in impairment of visual acuity and acquired hypogonadism. Baseline and stimulated serum cortisol levels were in the normal range. The finding of clearly elevated basal immunoradioassayable ACTH was unexpected in this patient, who initially was diagnosed as having a nonfunctioning chromophobe ad-

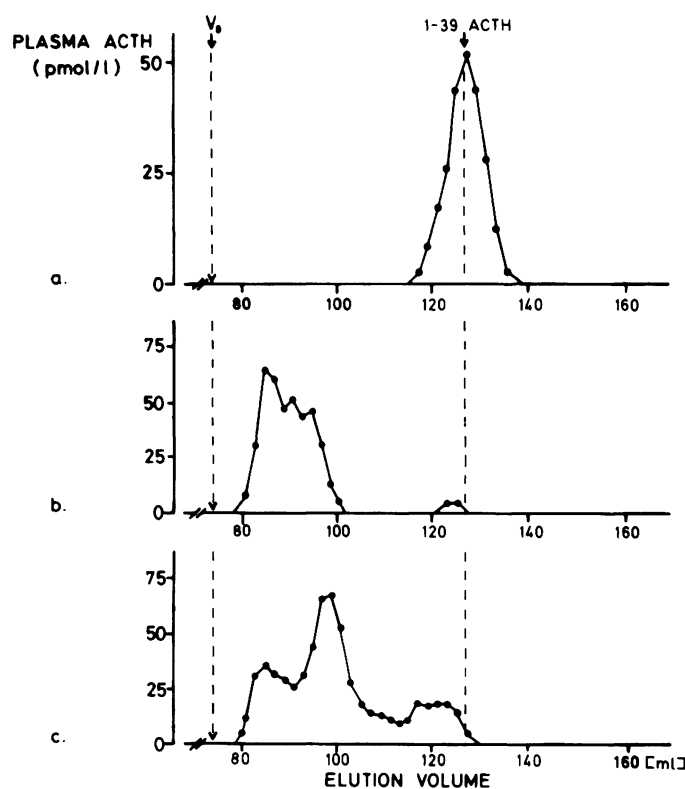


FIG. 2. Gel filtration patterns of plasma ACTH obtained (b) from our patient (b), a patient with Addison's disease (a), and a patient with the ectopic ACTH syndrome due to a bronchial carcinoma (c).  $V_0$ , Void volume.

enoma. Gel chromatography demonstrated that a high mol wt form of ACTH accounted for more than 95% of the immunoreactive ACTH detected. After incomplete removal of the tumor, ACTH levels remained elevated. The tumor recurred within 18 months, demonstrating the aggressive nature of the tumor.

ACTH and related peptides are produced and secreted by pituitary tumors in the context of Cushing's disease (13) and by extrapituitary tumors (ectopic ACTH-producing tumors) (14). Beside the main feature of hyper-

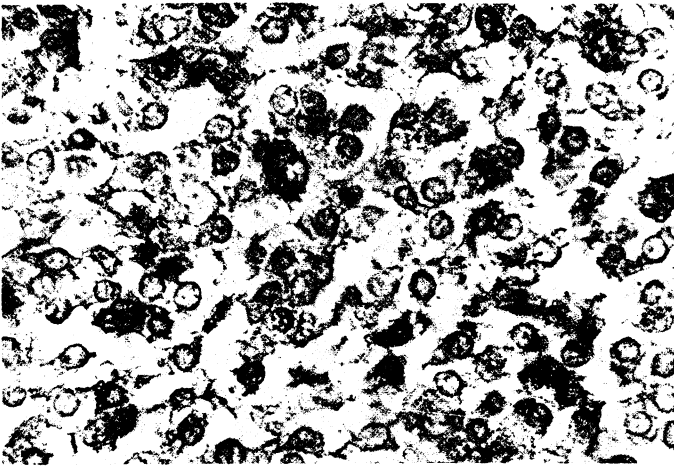


FIG. 3. Immunostaining for ACTH [anti-ACTH-(1-23)]. ACTH-positive granules are most prominently seen in the periphery of many adenoma cells. Anti-ACTH, peroxidase-antiperoxidase, diamino-benzidine. Magnification,  $\times 670$ .

cortisolism, abnormalities in the processing of the ACTH precursors have been found, resulting in the secretion of various large molecular forms of ACTH (15). These large forms of ACTH appear to be more typical of the ectopic ACTH syndrome (11). While there are a few recent reports of big ACTH secretion by aggressive pituitary adenomas in patients with Cushing's disease (14, 16-18), the production of big ACTH by a silent corticotropic pituitary adenoma has not been previously reported.

Silent corticotropic adenomas unassociated with clinical and biochemical signs of hormone overproduction have been well described. Such tumors were classified as chromophobe adenomas by conventional staining techniques, but contained immunoreactive ACTH (2, 5). In the series described by Horvath *et al.* (2) 43% of all corticotropic tumors were not associated with clinical signs of Cushing's disease, and 9 of 14 tumors examined histologically were of the chromophobe type. These tumors have several features in common with that in our patient, notably a relatively rapid growth rate and a high recurrence rate.

The cause of "silence" in these adenomas appears complex. In some tumors it has been attributed to failure of exocytosis of hormone from the cell membrane and to an increase in intracellular disposal by lysosomes (19). In other tumors, examination by electron microscopy suggested defective packaging of ACTH into secretory granules due to an inadequately developed Golgi complex (2). In our patient the cause appears to be incomplete or aberrant processing of proopiomelanocortin (POMC), the large precursor of ACTH, and, thus, failure to produce biologically active hormone. POMC is a 31,000-dalton glycoprotein and contains ACTH and  $\beta$ -lipotropin in its carboxy-terminal portion and an N-terminal protein of 16,000 daltons (pro- $\gamma$ MSH). Production of ACTH

and related peptides involves an intermediate step, wherein the C-terminal  $\beta$ -lipotropin is cleaved, followed by the cleavage of ACTH (20). In ectopic ACTH-producing tumors and less prominently in pituitary adenomas several abnormalities in the biosynthesis and processing of ACTH have been reported (21). In a report of ectopic ACTH production, cleavage of the N-terminal peptide from ACTH/ $\beta$ -lipotropin preceded cleavage between  $\beta$ -lipotropin and ACTH (22). In our patient, the increase in  $\beta$ -endorphin/ $\beta$ -lipotropin immunoreactivity in the presence of big ACTH in plasma may be due to a similarly abnormal ACTH/ $\beta$ -lipotropin peptide. Otherwise, elevated  $\beta$ -endorphin/ $\beta$ -lipotropin immunoreactivity may be explained by the secretion of  $\beta$ -endorphin/ $\beta$ -lipotropin and big ACTH simultaneously.

In patients with Cushing's syndrome due to a pituitary adenoma, ACTH responsiveness to vasopressin, metyrapone, bromocriptine, and dexamethasone persists, although it is quantitatively abnormal (13). In contrast, this man had poorly autonomous secretion of big ACTH. There was no response to bromocriptine or metyrapone, while plasma ACTH levels decreased somewhat during high dose dexamethasone. These abnormalities reflect the relative autonomy of the tumor.

The source of bioactivity in Cushing's syndrome with secretion of various molecular forms of ACTH is uncertain (16, 17). The bioactivity in the large mol wt fractions from ectopic tumors is assumed to be low (17). This patient's plasma contained big ACTH, which accounted for more than 95% of the detected immunoreactive ACTH. In the presence of normal serum cortisol levels and normal 24-h cortisol excretion this high mol wt form of ACTH probably had no or very little bioactivity.

In conclusion, this patient again demonstrates that abnormalities of POMC processing and secretion are not a unique feature of the ectopic ACTH syndrome. His illness confirms the observation of relatively rapid growth and high recurrence rates in silent corticotropic adenomas. In such patients with silent pituitary adenomas, screening for high mol wt ACTH should, therefore, be performed.

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