# Case Report: Acromegaly and Cushing's Disease in a Patient with Synchronous Pituitary Adenomas

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**ABSTRACT: A 40-year-old white woman presented with hirsutism, amenorrhea, generalized fatigue, diffuse weight gain, acral changes, and coarsened facial features. Physical examination revealed mild diastolic hypertension, acromegalic features, hirsutism, and seborrhea. The growth hormone concentration was elevated and did not suppress after glucose administration. Urinary free cortisol excretion was increased and was not suppressed during a 2 mg low-dose dexamethasone suppression test. Magnetic resonance imaging of the sella demonstrated a 1.3 × 1.2 × 0.8 cm pituitary adenoma. Trans-sphenoidal resection was performed, and portions of the resected tumor were analyzed by routine pathologic methods. Histopathologic and immunohistochemical findings indicated discrete growth hormone- and adrenocorticotropic hormone-producing pituitary adenomas. Coexisting acromegaly and Cushing's syndrome due to pituitary neoplasia was previously reported in two patients. However, to the authors' knowledge, this represents the first description of a patient with acromegaly and Cushing's disease resulting from discrete synchronous adenomas of the pituitary gland as defined by modern histopathologic techniques. KEY INDEXING TERMS: Acromegaly; Cushing's syndrome; Multiple adenomas; Pituitary neoplasm; Plurihormonal adenoma. [Am J Med Sci 1992; 304(5):294–297.]**

The simultaneous occurrence of Cushing's syndrome and acromegaly is rare. A recent review of the literature identified reports of two individuals with the coexistence of these syndromes that probably resulted from a pituitary tumor.[1–3] However, morphologic features characteristic of growth hormone and adrenocorticotropic hormone (ACTH) production could not be conclusively demonstrated in these tumors because of limitations in histopathologic techniques. Advances in immunohistochemistry, electron microscopy, and molecular biology have since provided significant insight into the functional and morphologic classification of the normal and abnormal pituitary gland.[4] We used immunohistochemical techniques to demonstrate the presence of synchronous growth hormone- and ACTH-producing pituitary adenomas in a patient with acromegaly and Cushing's syndrome. In this report, we describe the clinical and pathologic features of this patient and review plurihormonal neoplastic disorders of the pituitary gland.

## Case Report and Hormonal Studies

A 40-year-old white woman presented with 2 years of progressive hirsutism and 6 months of amenorrhea. She denied other features of masculinization. Review of her systems disclosed generalized fatigue, a 18 kg diffuse weight gain, diaphoresis, oily skin, swelling of the hands and feet, and coarsening of facial features. She denied other features of glucocorticoid and growth hormone excess, headache, and visual disturbances. There was no suggestion of familial multiple endocrine neoplasia.

Physical examination revealed she was acromegalic, with a blood pressure of 130/95 mm Hg, pulse 80 beats/min, respiration 18/min, and weight 82 kg. There was photographic evidence of progressive coarsening of facial features. Visual fields were normal by confrontation, and cranial nerve function was intact. Acne and seborrhea were on the face. Terminal hairs were distributed over the lower back, inner thighs, buttocks, and anterior abdomen with a male escutcheon pattern. There were no signs of virilization. The remainder of the examination was remarkable for the absence of abdominal masses, organomegaly, muscle weakness, striae, ecchymoses, galactorrhea, and other findings of hormonal hypersecretion.

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Routine laboratory investigation (Table 1) disclosed an increase in urinary free cortisol excretion that was not suppressed after a standard low dose dexamethasone suppression test (dexamethasone 2 mg by mouth every 6 hours for 48 hours). Mild hyperandrogenemia was present. An investigation of pituitary function (Table 2) disclosed an elevated random growth hormone concentration that was not suppressed after oral glucose administration (100 g). All hormonal studies were performed using standard commercial assay kits.

A diagnosis of acromegaly and Cushing's syndrome was made. The patient refused additional diagnostic studies to characterize the hypercortisolism. Magnetic resonance imaging of the sella with gadolinium enhancement demonstrated a 1.3 × 1.2 × 0.8 cm pituitary adenoma. Trans-sphenoidal resection of the pituitary macroadenoma was performed without complication. Tumor fragments were obtained for pathologic analysis.

Laboratory evaluation 3 months postoperative disclosed a urinary free cortisol excretion of 309 nmol/d and a fasting growth hormone level of 0.8 μg/L. Urinary free cortisol excretion was suppressed normally during a low-dose dexamethasone suppression test. Six months postoperative, the patient noted a decrease in the soft tissues of her face and hands, resumption of cyclical menses, and a diminution in terminal hair growth.

**Pathologic Analysis.** A portion of the resected tissue was fixed in 10% phosphate buffered formalin, paraffin embedded, and routinely processed for light microscopy. Five-micron tissue sections were stained by the hematoxylin-eosin and Gomori's reticulin methods. For immunohistochemistry, additional sections were reacted with the following antibodies using the streptavidin-horseradish peroxidase conjugate technique:[5] human growth hormone (mouse monoclonal, 1:3000 dilution; Biogenex, San Ramon, CA); prolactin (rabbit polyclonal, prediluted by manufacturer; Biogenex), and ACTH (rabbit polyclonal, 1:3000 dilution; Biogenex). Appropriate negative controls using nonimmune antisera and positive controls were studied simultaneously.

Hematoxylin-eosin-stained sections revealed disorganized sheets of polygonal cells with small round nuclei. No normal pituitary parenchyma was present. Two distinct cell populations, separated by a broad band of fibrous tissue, were identified. The larger population measured approximately 0.7 cm in greatest its dimension and predominantly consisted of cells with densely granulated eosinophilic cytoplasm (Figures 1 and 2). The reticulin stain demonstrated loss of the normal pituitary connective tissue architecture, consistent with an adenoma. This population of cells had diffuse intense immunoreactivity for antibody to growth hormone and negative staining for ACTH (Figures 3 and 4). Rare isolated cells reacted for prolactin. The second distinct cell population measured approximately 0.1 cm and was composed exclusively of a sheet of cells with amphophilic cytoplasm. The distorted reticulin network of this region also was consistent with an adenoma. Immunohistochemistry demonstrated strong diffuse ACTH staining and negative reactions for prolactin and growth hormone (Figures 3 and 4). No interconnection between these lesions was identified on serial tissue sections. This constellation of histopathologic and immunohistochemical findings indicated discrete growth hormone- and ACTH-producing pituitary adenomas.

**Table 1.** Results of the Hormonal Evaluation of Hirsutism

| | Result | Normal Range |
|---|---|---|
| Testosterone, total | 187 nmol/L | 52–243 |
| Testosterone, free | 32 nmol/L | 3.5–29.5 |
| Dehydroepiandrosterone-S | 4.4 μmol/L | 1.4–3.8 |
| Urine 17-ketosteroids | 62 μmol/d | 17–52 |
| Urine-free cortisol | 731 nmol/d | 66–298 |
| 2 mg low-dose dexamethasone suppression test | | |
| Urine-free cortisol | 166 nmol/d | <69 |

**Table 2.** Results of the Hormonal Evaluation of Pituitary Function

| | Result | Normal Range |
|---|---|---|
| Luteinizing hormone | 16 IU/L | 0–10 |
| Follicle stimulating hormone | 15 IU/L | 3–15 |
| Prolactin | 9 μg/L | 2–27 |
| Alpha subunit | 0.4 μg/L | <3.6 |
| Thyroid stimulating hormone | 0.6 IU/L | 0.2–3.2 |
| Thyroxine | 99 nmol/L | 52–149 |
| Triiodothyronine uptake | .23 | .22–.35 |
| Growth hormone, random | 46.5 μg/L | <5 |

| | Basal | 1 hr | 2 hr |
|---|---|---|---|
| Oral glucose tolerance test, 100 g dextrose | | | |
| Growth hormone (μg/L) | 22 | 18 | 22 |
| Glucose (mmol/L) | 99 | 113 | 103 |

## Discussion

The present report represents the first description of a patient with discrete synchronous adenomas of the pituitary resulting in acromegaly and Cushing's disease. A diagnosis of acromegaly was firmly supported by the available clinical, hormonal, and pathologic data. A diagnosis of Cushing's disease was supported by incomplete suppression of the elevated urinary free cortisol excretion during a standard low-dose dexamethasone suppression test and the conclusive demonstration of an ACTH-producing pituitary adenoma. Mild hirsutism, hyperandrogenemia, and an elevation in urinary free cortisol excretion often are associated with acromegaly.[6–8] However, the enhanced cortisol excretion typically is modest and generally is suppressed after dexamethasone administration, revealing normal feedback sensitivity of the hypothalamic-pituitary-adrenal axis.[7,8]

In 1951, McCormick et al[1] described a patient with clinical features of excessive growth hormone and glucocorticoid secretion, nodular adrenal hyperplasia, and a pituitary tumor with light microscopic features characteristic of an acidophilic adenoma. This adenoma was believed responsible for the development of Cushing's syndrome based on the demonstration of elevated

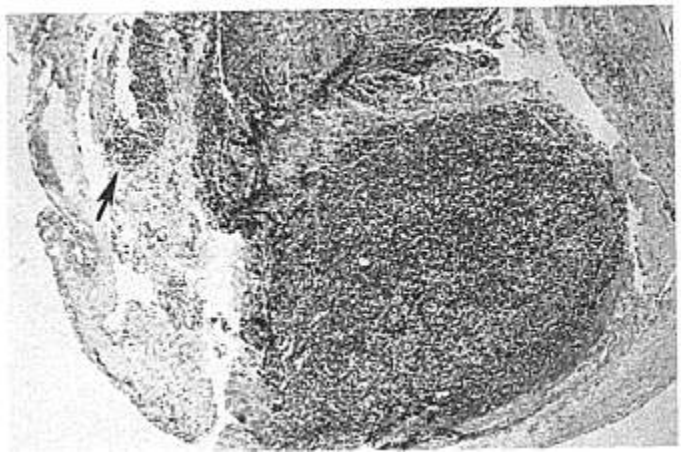

**Figure 1.** Two discrete adenomas. One is composed predominantly of eosinophilic cells, and the other (arrow) is composed exclusively of amphophilic cells. (Hematoxylin-eosin; original magnification ×65.)

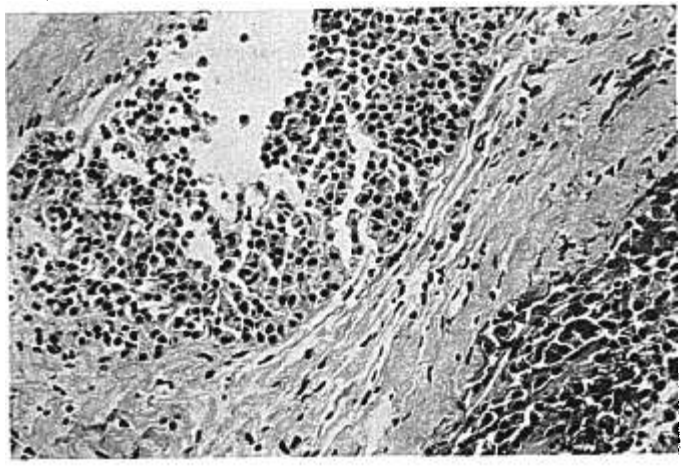

**Figure 2.** Adjacent regions of the adenomas, separated by a broad band of fibrous tissue. (Hematoxylin-eosin; original magnification ×320.)

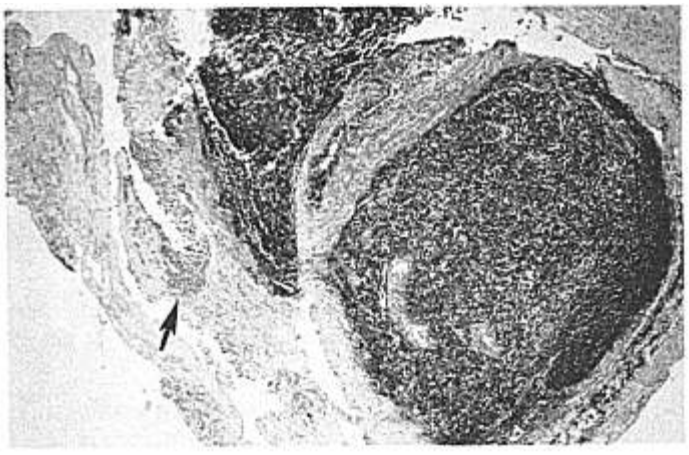

**Figure 3.** Section reacted with anti-growth hormone demonstrates a strong positive reaction in the larger adenoma and a negative reaction in the smaller one (arrow). (Original magnification ×65.)

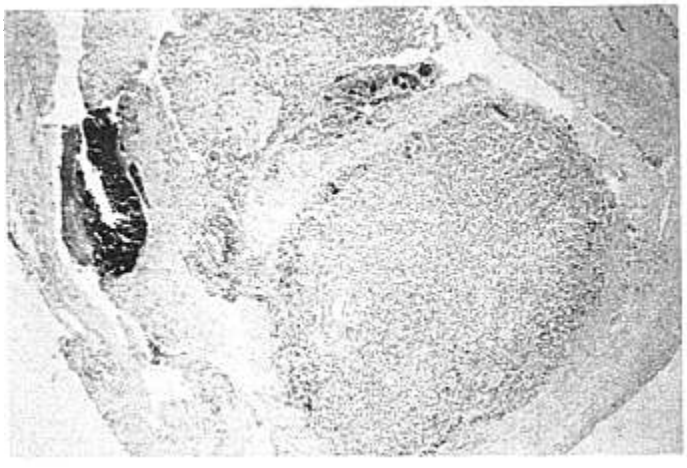

**Figure 4.** Section reacted with anti-ACTH demonstrates intense positive staining limited to the smaller adenoma. (Original magnification ×65.)

serum ACTH bioactivity, which declined after partial hypophysectomy. In 1970 and in 1978, Scriba et al[2,3] reported on a patient with acromegaly, Cushing's syndrome, and hyperprolactinemia that presumably resulted from a single pituitary adenoma. Limitations in histopathologic techniques prevented a precise determination of the functional morphology of the pituitary tumor or tumors in each of these patients. Furthermore, the simultaneous occurrence of these syndromes has been described in other clinical situations. Leveston et al[9] reported an individual with acromegaly and Cushing's syndrome due to a foregut carcinoid tumor that secreted growth hormone, growth hormone-releasing hormone, and ACTH. Gorden et al[10] reported a patient with acromegaly due to a pituitary tumor who later developed Cushing's syndrome secondary to ectopic ACTH secretion from a bronchial carcinoid tumor. Finally, Rosenzweig et al[11] reported a patient with a growth hormone secreting pituitary tumor and ACTH-independent hypercortisolemia. This patient demonstrated other features that suggested the Carney complex.[12]

Multiple adenomas of the pituitary gland have been reported in approximately 0.9% of random autopsy pituitary samples.[13] These tumors typically are microadenomas, and clinical evidence for hormonal hypersecretion usually is absent. Silent corticotroph adenomas have been detected in pituitary glands that also harbored nonfunctional adenomas.[13] Tolis et al[14] described a patient with acromegaly and hyperprolactinemia resulting from synchronous growth hormone- and prolactin-secreting tumors. Generally, a plurihormonal pituitary adenoma should be suspected when clinical or biochemical hypersecretion of two or more adenohypophysial hormones is present.[15]

Clinically apparent pituitary adenomas are plurihormonal in 10–15% of cases.[15,16] Plurihormonal adenomas may consist of one cell type secreting multiple

hormones (monomorphous) or of several cell types, each secreting one hormone (plurimorphous).[4] The most frequently occurring plurihormonal adenomas cosecrete growth hormone and prolactin.[4,15,16] Thirty to fifty percent of individuals with acromegaly are hyperprolactinemic. These tumors include mixed growth hormone and prolactin cell adenomas, mammosomatotroph (growth hormone predominant) adenomas, and acidophil stem cell (prolactin predominant) adenomas.[4,15,17-20] Adenomas that cosecrete growth hormone and the glycoprotein hormones (luteinizing hormone, follicle stimulating hormone, thyroid stimulating hormone, and alpha-subunit) also are well described.[21-23] Generally, ACTH-secreting plurihormonal adenomas are rare.[4] However, ACTH- and prolactin-secreting plurimorphous adenomas and monomorphous adenomas that secrete ACTH and alpha-subunit have been reported.[24-27] Glycoprotein-secreting tumors that also secrete alpha-subunit, and ACTH-secreting tumors that release other peptides cleaved from proopiomelanocortin, are not classified as plurihormonal adenomas.[15]

Plurihormonal pituitary adenomas are more commonly recognized by histopathologic and immunocytochemical analysis than by standard clinical evaluation.[4] Discordant morphologic and clinical findings may result from hormone synthesis with impaired secretion, intracellular degradation, or altered bioactivity.[15] Horvath and Kovacs[4] recommended reserving the diagnosis of a plurihormonal pituitary adenoma for those instances when more than one of the expressed hormones results in clinical symptoms or when the expression of each hormone is associated with the presence of well-defined morphologic cell types.

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