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Hyperandrogenemia and Virilization with Simultaneous Pituitary and Adrenal Adenomas

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We describe a postmenopausal woman who presented with virilizing hyperandrogenemia and was found to have an intrasellar tumor and a large left adrenal mass. Pathologic studies showed an undifferentiated hypophyseal adenoma with immunostaining for chromogranin only and a benign adrenocortical adenoma. In light of current understanding of the regulation of adrenal androgen secretion and adrenocortical mitogenesis, we postulate that this case may be explained by secretion of adrenal androgen-stimulating and mitogenic factors by the pituitary tumor. (Henry Ford Hosp Med J 1991;39:22-4)

“...No other single structure in the body is so doubly protected, so centrally placed, so well hidden. Her acts being purposeful, nature must have had abundant reason for this, and man’s prying curiosity impels him to ask what they were.” (Harvey Cushing, 1930) (1)

Considerable evidence supports the existence of pituitary-derived factors other than adrenocorticotropic hormone (ACTH) which modulate adrenal androgen secretion (2-5) and exert mitogenic effects on the adrenal cortex (6,7). We describe a postmenopausal woman who presented with hyperandrogenemia and virilization and was found to have simultaneous benign pituitary and adrenal neoplasms. The pathophysiology underlying this unusual case may relate to such pituitary-derived factors and thereby represent an endocrinologic syndrome.

Case Report

Patient summary

A 64-year-old woman developed progressive hirsutism and frontotemporal balding following menopause at age 56. She first presented to her physician for evaluation in September 1976. Blood pressure was 170/100 mm Hg, and she was noted to have truncal obesity, bilateral papilledema, and abnormal glucose tolerance.

Upon referral to Henry Ford Hospital, examination revealed striking male facial appearance (Fig 1A), body hair distribution, and mild clitoromegaly. Features of Cortisol excess were not present. Endocrine studies included 24-hour urinary cortisol (195 nmol [normal < 330 nmol]), 17-hydroxycorticosteroids (25 µmol [normal < 22 µmol]), and 17-ketosteroids (17-KS) (410 to 520 µmol [normal < 70 µmol]). Serum testosterone was 5.3 nmol/L (normal 0.7 to 2.4 nmol/L) with dehydroepiandrosterone-sulfate (DHEA-S) levels at 20,000 to 30,500 µg/L (normal 200 to 3,350 µg/L). Plasma ACTH was 14 to 20 pmol/L (normal < 26 pmol/L) with serum prolactin 34.4 µg/L (normal < 20 µg/L) and suppressed gonadotropin levels. Thyroid function tests were normal. Intravenous pyelography with nephrotomograms and subsequent angiography showed a hypervascular 4 x 8 cm left adrenal mass. Computed tomography showed an intrasellar pituitary tumor with mild suprasellar extension; visual field testing was intact.

Transsphenoidal hypophysectomy was performed with apparent complete resection of an obvious adenoma. Severe pancreatitis ensued, possibly related to perioperative glucocorticoid therapy. Left adrenalectomy was performed one month later without complications. The right adrenal was normal by palpation and was not biopsied.

Postoperatively, masculine features gradually receded (Fig 1B) as did papilledema, androgen and 17-KS levels normalized. Mild hypotension and hyperprolactinemia (42 to 63 pg/L while taking α-methyl/dopa and tricyclic antidepressants) persisted with preserved anterior pituitary function. During 13 years of subsequent follow-up, no recurrence of either tumor has occurred.

Pathologic studies

The pituitary tumor was composed of uniform cells with granular cytoplasm. Immunohistochemical studies, performed in 1985, disclosed specific immunoreactivity for chromogranin in individual cells; immunostaining for α-melanocyte-stimulating hormone (MSH), β-MSH, prolactin, β-endorphin, ACTH, and leucine-enkephalin was negative. These findings were consistent with a null cell or undifferentiated pituitary adenoma. The encapsulated adrenal tumor was hemorrhagic and composed of well-differentiated pleomorphic polygonal cells with prominent nucleoli, occasional mitoses, and minimal necrosis. Adrenocortical tumor cells did not display immunoreactivity for any of the polypeptide hormones mentioned above.

Discussion

Few well-documented cases of simultaneous pituitary and adrenocortical adenomas have been reported (8-11); all of these were associated with cortisol excess. To our knowledge, our pa-
tient is unique in having severe androgen excess and virilism without ACTH hypersecretion accompanying the dual tumors. Although possibly coincidental, we believe that the pituitary and adrenal neoplasms in this patient may be interrelated.

Several experimental and clinical findings suggest that ACTH is not the sole modulator of adrenal androgen secretion (3). The dramatic increases in serum DHEA and DHEA-S (12) and accompanying differentiation and growth of the zona reticularis (13) that constitute adrenarche (and later decline in adrenopause) occur without alterations in ACTH or cortisol levels. Bovine pituitary extract induces greater adrenal androgen secretion than ACTH preparations in the castrated dexamethasone-suppressed dog (14), and DHEA-S levels are suppressed despite maintenance of cortisol production in the hypophysectomized ACTH-replaced chimpanzee (5). The putative adrenal androgen-stimulating factor (2-4) appears distinct from gonadotropins (15), growth hormone (16), prolactin (16), β-lipotropin (16), β-endorphin (16,17), and α-MSH (16). This factor may induce 17,20-desmolase and sulfatase enzymatic activity (and perhaps suppress 3β-hydroxysteroid dehydrogenase activity); alternatively, an adrenarchal factor may solely stimulate development of the zona reticularis which possesses enzymatic function and response to ACTH intrinsically distinct from that of the zona fasciculata (18). The hinge-portion of N-terminal proopiomelanocortin (POMC) has been identified as having potent stimulator effects on DHEA production by human adrenal cells that are potentiated by ACTH (19).

Likewise, adrenocortical mitogenesis may be mediated by factor(s) other than ACTH itself (7). ACTH inhibits adrenocortical cell proliferation in vitro (20), while anti-ACTH antiserum does not cause adrenal atrophy (6,21) nor alter compensatory adrenocortical hyperplasia occurring in rats after unilateral adrenalectomy (21). Pro-γ-MSH N-terminal POMC peptides have potent mitogenic effects on the adrenal in vitro and in vivo (6,22). Mitogenically active N-terminal POMC peptides also appear to be physiologically important in adrenal regeneration after bilateral adrenal enucleation in rats (23). N-terminal POMC also enhances adrenocortical responsiveness to ACTH (24).

Also pertinent to this case is the suggestion that long-standing adrenocortical hyperplasia may predispose to adenoma formation (8-11). Macronodular adrenocortical hyperplasia in Cushing's disease (25) may be a transitional state in this regard (10, 11). We have reported a patient with Cushing's disease and macronodular hyperplasia who had marked elevation of serum DHEA-S (26). We hypothesized that chronic cosecretion of adrenal androgen-stimulating and adrenocortical mitogenic factors with ACTH may underlie the pathophysiology in this unusual case.

Fig 2 shows a similar pathophysiologic explanation proposed for the present case which was not accompanied by ACTH hypersecretion or hypercortisolism. We postulate that secretion of adrenal androgen-stimulating and adrenocortical mitogenic factors by the pituitary tumor could account for the clinical features observed in this patient—severe hyperandrogenemia and adrenal adenoma formation over time. Selective hypersecretion of non-ACTH POMC peptides by pituitary tumors is not without precedent (27). We predict that this syndrome will be further substantiated by careful investigation (including high-resolution pituitary and adrenal imaging) of a subset of women presenting with severe adrenal hyperandrogenemia (serum DHEA-S > 8,000 to 10,000 μg/L), hirsutism with or without virilization, and oligomenorrhea. Further characterization of the structure and function of these factors in the future will likely provide

Fig 1—Facial appearance of a patient with virilization and simultaneous pituitary and left adrenal adenomas: A) preoperatively in December 1976; B) postoperatively in January 1979.
Fig 2—Proposed pathophysiologic diagram showing possible adrenal effects of pituitary-derived adrenal androgen-stimulating and adrenocortical mitogenic factors.

major insight into the possibly related physiologic processes—adrenarche and control of the fetal adrenal as well as pathologic alterations in adrenocortical mass and steroidogenesis.

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References