Multiple secreting microadenomas as a possible cause of selective transsphenoidal adenomectomy failure

Case report

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Approximately 10% to 20% of patients who undergo selective transsphenoidal removal of secreting microadenomas fail to achieve a cure. One of the possible causes of these failures is multiple adenomas. A case history is presented of two microadenomas within the same gland, and the multiplicity of pituitary adenomas is discussed.

KEY WORDS • multiple adenomas • transsphenoidal surgery • adenomectomy • treatment failure

WITH selective transsphenoidal removal of microadenomas, 80% to 90% of patients will experience a complete resolution of symptoms and signs, with return of the elevated hormones to normal levels.1,6,8,14,17,18,20,23,24 Although the overall results of surgical management of microadenomas are good, 10% to 20% of the patients fail to be cured. Possible explanations for these failures are: incomplete removal, diffuse hyperplasia, and multiple adenomas.18 Little attention has been given to the multiplicity of these tumors even though it is a well documented finding in postmortem examinations of the pituitary gland. A patient found to have two microadenomas within the same gland is presented, and multiple adenomas are discussed as a possible explanation of a number of surgical failures.

Case Report

This 23-year-old black woman was referred for further evaluation of the amenorrhea-galactorrhea syndrome. She had experienced menarche at 16 years old and had a spontaneous abortion at age 17 years. She then began oral contraceptives, discontinuing them at 19 years old, after which she delivered a normal child. She then resumed oral contraceptives until 6 months prior to admission. The first 3 months after discontinuing oral contraceptives, she experienced oligomenorrhea followed by amenorrhea, galactorrhea, and mild bifrontal headaches. She denied loss of libido, visual change, or other neurological symptoms. Past medical history was unremarkable, and there was no history of recent medications.

Examination. Physical examination was normal except for diffuse milky discharge from both breasts. Thyroid panel was normal. The fasting a.m. cortisol level was 9.5 μg/ml (normal 7 to 25 μg/ml), thyroid-stimulating hormone (TSH) 3.3 μIU/cc (normal < 7.3 μIU/cc), follicle-stimulating hormone 12 mIU/ml (normal 5 to 15 mIU/ml), and prolactin 160 ng/ml (normal 2 to 25 ng/ml). Stimulation of TSH by thyrotropin-releasing hormone resulted in TSH levels of 2.0, 30, 31, and 32 μIU/ml, with the prolactin response being 164, 176, 176, and 184 ng/ml at 0, 20, 40, and 60 minutes, respectively. Cortisone responses to insulin-induced hypoglycemia were 6.6, 30.5, and 31.5 ng/ml, and human growth hormone (HGH) was 1.1, 8.1, and 22.2 ng/ml at 0, 45, and 120 minutes, respectively (normal baseline level < 5 ng/ml). Polytomography and computerized tomography revealed slight expansion of the sella turcica on the right side.

Operation. The patient underwent transsphenoidal exploration of the pituitary fossa, and two distinct
tumors were found, one in the right lateral wing measuring 2 x 2 x 2 mm and the second in the left lateral gland measuring 3 x 3 x 4 mm. Careful dissection revealed these to be separate tumors very near the surface, with the main body of the gland interposed between them.

Postoperative Course. The postoperative course was uneventful, and on the 4th postoperative day the serum prolactin level was 54 ng/ml. Twenty months later, the patient's serum prolactin was 80 ng/ml, the thyroid panel was normal, and a.m. and p.m. cortisol levels were 16.7 and 10 μg%, respectively. Her amenorrhea and galactorrhea persisted, although the latter was diminished.

Pathological Examination. The two tumors were studied by both light microscopy and immunohistochemistry. Histologically, both neoplasms were chromophobe pituitary adenomas. They were composed of epithelial cells in sheets with oval hyperchromatic nuclei. No cytoplasmic granules were demonstrable with the Ezrin-Wilson stain, and there was loss of the normal reticular pattern. Biopsies of the grossly normal intervening gland and both tumor beds showed no histological evidence of tumor. Sections of both adenomas and the intervening normal gland were stained immunocytochemically for adrenocorticotropic hormone (ACTH), prolactin, HGH, and β-endorphin. Cells staining for ACTH, prolactin, and β-endorphin were found in the normal pituitary tissue. Both adenomas stained positive for prolactin and were negative for the other hormones.

Discussion

There have been two previous reports of multiple adenomas occurring simultaneously in the same patient during surgery. Tolis, et al.,22 described a patient who had an HGH-secreting tumor in the presence of a prolactinoma. Both were excised separately. Powers and Wilson17 found two adenomas in a patient with marked prolactinemia. Both stained positive for prolactin and to a lesser degree for HGH on immunofluorescence. They considered multiple adenomas to be a rare clinical entity, having not encountered this phenomenon in some 600 operations for pituitary adenomas resected transphenoidally.17 This is in contrast to numerous autopsy series in which both single and multiple clinically silent pituitary adenomas were found2,3,8,9,11,12,13,15,16 (Table 1). The incidence of glands harboring tumors has varied from 8.3% to 27%, with 0.01% to 9% of the glands having multiple adenomas. However, in only two of these studies was the gland sectioned in its entirety, which should reflect a totally accurate occurrence rate. In 1936, Costello5 performed free-hand sections 1 to 1.5 mm apart, finding a 4% incidence of multiple adenomas. A few glands had more than two tumors, and in one gland 10 tumors were identified. More recently, Burrow, et al.,2 found a 9% incidence of multiple tumors when making 1-mm serial sections. They defined adenomas as a mass of uniform cells having a stromal pattern different from the surrounding gland, with evidence of compression of the adjacent pituitary parenchyma. Focal lesions not meeting these criteria were termed "hyperplasia" and were not included. It appears that the tumors found post mortem were no different from ones found during life. Mosca, et al.,13 in a histochemical, ultrastructural, and histopathological study, compared 66 tumors removed surgically with 24 microadenomas in 100 pituitaries removed at autopsy, and found the same type of tumor cells in both groups. Based upon these pathological studies and the case reported here, it is possible that a portion of the patients who fail to be cured by selective adenomectomy may be harboring a second tumor.

Multiplicity of tumors may be associated more commonly with hyperprolactinemia and estrogen exposure, as in the case reported here. A number of investigators (including Fulling KH, et al.: personal communication, 1982) have demonstrated that, with the prolonged administration of estrogens to animals, the pituitary becomes diffusely enlarged, with hyperplasia of the prolactin cells and development of multinodular adenomatous lesions composed of prolactin cells.5 Whether this is true in humans is the subject of much debate.4,20 Estrogen receptors and the association of high levels of endogenous estrogens in prolactin cells has been demonstrated in human pituitary adenomas (Takei Y, et al.: personal communication, 1982). In a series of 22 patients with microprolactinomas, we found that the 15 who had used oral contraceptives had a cure rate of 56%, whereas the seven patients without estrogen exposure achieved a 100% cure rate by adenomectomy.25 In reviewing cure rates for secreting microadenomas, one is struck by the lower rate for prolactinomas (77%2,1,14,16,21,23,25,26) as compared to the HGH tumors (82%)6,8,23 that are sometimes associated with hyperprolactinemia, and ACTH adenomas (86%).16,23,24

When an obvious tumor is found at the initial
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operation for microadenoma, it is recommended that the entire anterior and lateral surface of the gland be exposed and inspected for a second tumor. According to autopsy and surgical series, approximately 50% of microadenomas will present on the surface. Keeping in mind the location of tumors as described by Hardy, one should inspect the lateral aspects of the gland more closely in patients with hyperprolactinemia and acromegaly, and the central portion in patients with Cushing's disease. In exploring a patient with hyperprolactinemia and prolonged exposure to estrogen, one may consider making an exploratory incision into the lateral wings of the gland to search for a second tumor if on inspection the surface appears normal.

References

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