FSH-producing macroadenoma associated in a patient with Cushing's disease

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Abstract

OBJECTIVE AND IMPORTANCE: We encountered a Cushing's disease patient whose surgically removed pituitary macroadenoma was not an ACTH-producing, but rather a gonadotroph adenoma. Cure was obtained only after a tiny microadenoma, overlooked on preoperative studies, was removed by a 2nd operation from a compressed thin normal anterior pituitary gland.

CLINICAL PRESENTATION: This 45-year-old woman with Cushing syndrome presented with diabetes mellitus and steroid psychosis. Endocrinological examinations suggested Cushing's disease and MRI disclosed an invasive macroadenoma (22 mm in diameter) with suprasellar extension.

INTERVENTION: Despite total removal of the invasive macroadenoma by transsphenoidal surgery, her elevated serum cortisol- and ACTH levels failed to decrease. Histologic study of the surgical specimen disclosed that the tumor was a silent FSH-producing, rather than an ACTH-producing adenoma. Detailed re-evaluation of pre- and postoperative MRI suggested the presence of a 3-mm microadenoma on the left side of a thin compressed normal gland. Venous sampling of the cavernous sinus confirmed this suspicion. In a 2nd operation an ACTH-producing microadenoma was removed from inside the thin remaining compressed normal pituitary gland and endocrinological cure of Cushing's disease was achieved.

CONCLUSION: Although double adenomas, being a non-ACTH producing macroadenoma associated with an ACTH producing tiny microadenoma, are extremely rare in patients with Cushing's disease, detailed preoperative MRI evaluation is necessary to avoid missing tiny adenomas hidden in a compressed normal pituitary gland which is the cause of Cushing's disease, especially when a macroadenoma is found in patient with Cushing's disease.

CASE REPORT

Case report

This 45-year-old woman was admitted to Saitama Medical Center for diabetes screening. Her clinical features, e.g. moon face, central obesity, and acne suggested Cushing's syndrome. Her serum ACTH- and cortisol levels were 80.9 pg/ml and 23.2 μg/dl, respectively. The overnight low-dose (1 mg) dexamethasone test (DST) did not, but high-dose (8 mg) DST did, suppress her serum cortisol. Her hypercortisolism was further confirmed by documenting the urinary excretion of elevated free cortisol (255 mg/24 hr) and loss of the normal circadian rhythm of cortisol secretion. Serum ACTH was elevated by CRH administration (pre-administration, 67.2 pg/ml; peak, 168 pg/ml). The results of endocrinological examinations suggested Cushing's syndrome due to ACTH-producing pituitary adenoma.

MRI disclosed an invasive, 22 × 13 × 15 mm pituitary macroadenoma that compressed the normal pituitary gland at the top and left side (Figure 1).

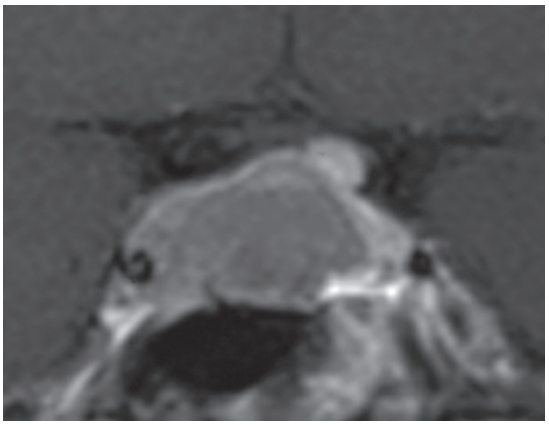

Figure 1. MRI revealed a pituitary macroadenoma with suprasellar extension. The normal gland was compressed to the left side of the *sella turcica*.

Based on these endocrinological and neuroimaging findings, a diagnosis of Cushing's disease due to pituitary macroadenoma was made and she was referred to our hospital for surgical treatment. An additional invasive examination, cavernous venous sampling, was not performed in this patient, since both endocrine data and neuroimaging of pituitary strongly indicated Cushing's disease. She underwent transsphenoidal surgery and the invasive macroadenoma was completely removed. However, neither her postoperative serum ACTH nor cortisol levels changed at all. In addition, the histologic examination disclosed that the resected tumor was an FSH- rather than an ACTH-producing pituitary adenoma (Figure 2).Detailed re-evaluation of pre- and postoperative MRI suggested the presence of a 3-mm microadenoma on the left side in a thin compressed normal gland (Figure 3). Venous sampling of the cavernous sinus under CRH administration strengthened this suspicion; the ACTH levels in the left cavernous sinus were markedly elevated before and after CRH administration (pre: 478.2 pg/ml, post: 4 662.2 pg/ml) compared to the right cavernous sinus (pre: 45.6 pg/ml, post: 245 pg/ml) and peripheral vein (pre: 10.0 pg/ml, post: 111.2 pg/ml). Based on these and our MRI findings we strongly suspected the presence of an ACTH-producing microadenoma in the normal gland on the left side. Thus she underwent a 2nd operation and a microadenoma was removed from inside the thin remaining compressed normal pituitary gland. Postoperatively, she manifested endocrinological cure of Cushing's disease; her postoperative serum cortisol level was less than 1.2 μg/dl. The tumor was a basophilic, PAS-positive adenoma; most adenoma cells were immunopositive for ACTH (Figure 4).

Discussion

Multiple pituitary adenomas are rare; in an autopsy series the incidence was approximately 1% [1]. These tumors have also been detected among surgical specimens; the reported incidence among operated patients was 0.17–1.8% [2–6]. The varied rate among surgical cases may reflect differences in the patient population, the institutional referral patterns, and differences in surgical procedures [5].

Multiple pituitary adenomas can be divided into two types; contiguous or clearly separated [3]. Most contiguous tumors are surgically removed as one tumor; their discernment as double adenomas is difficult on preoperative MRI. Therefore, a correct diagnosis of multiple adenomas requires histologic examination. On the other hand, most clearly-separated pituitary adenomas can be diagnosed on preoperative MRI study [2,3,5–8].

Hence most of the reported double adenomas were combination with GH-producing and clinically nonfunctioning [4,5,9–11,13], Cushing's disease patients with double adenomas also have been documented [2,6,7,10,14–16]. In the series of Ratliff and Oldfield [5], 13 of 660 (2.0%) operated patients with Cushing's disease had multiple adenomas; in 10 (1.5%) their presence was identified by operative findings or postoperative histopathologic results. In only 1 case (0.15%) were multiple adenomas diagnosed on preoperative MRI; the double adenoma was comprised of a 15-mm diameter PRL-producing macroadenoma and an 8-mm diameter ACTH-producing microadenoma located on both sides of the pituitary gland. Booth et al. [10] also reported clearly-separated double adenomas composed of an ACTH- and a PRL-producing adenoma in a Cushing's disease patient; these tumors were diagnosed by inferior petrosal sinus sampling and operative findings, they were not recognized on preoperative MRI. The other reported double adenomas in patients with Cushing's disease were contiguous tumors and confirmed by histological examination.

The double adenomas in our patient were separate tumors discernible by careful inspection of preoperative MRI. She was the only among 1000 patients (0.1%) with pituitary tumors treated at our institute who manifested

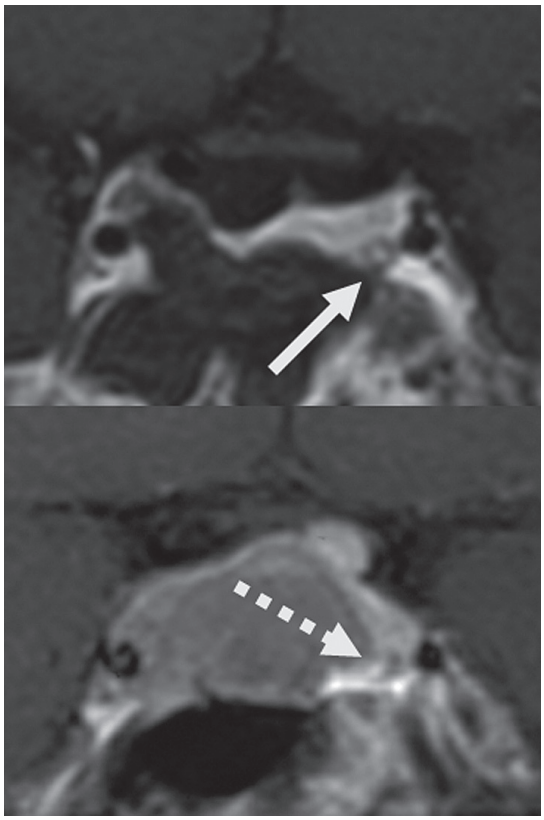

Figure 3. MRI, obtained after the 1st operation, confirmed the total removal of the macroadenoma, and suggested the presence of a microadenoma (arrow) in the compressed normal gland, which was also recognized on preoperative MRI (dot arrow).

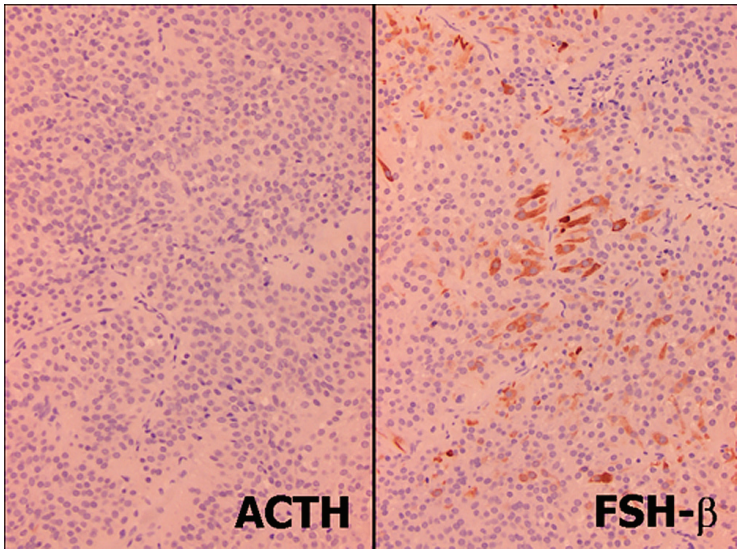

Figure 2. Immunohistochemical examination of the removed macroadenoma revealed it to be FSH- positive and ACTH-negative (original magnification × 200).

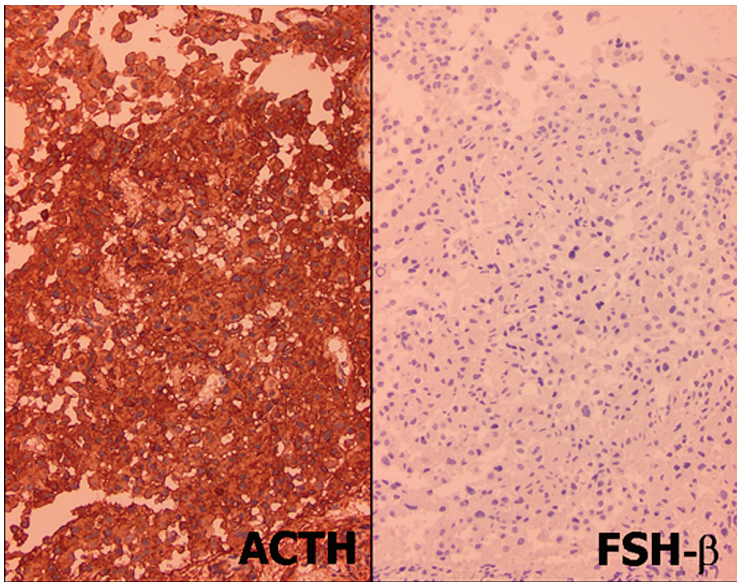

Figure 4. Pathologically, the microadenoma removed by a 2nd operation from a compressed thin normal anterior pituitary gland was an ACTH-producing tumor (original magnification × 200). Postoperative endocrinological study confirmed the complete remission of Cushing's disease.

Cushing's disease and double adenomas. Although, as in the 2 patients reported by Ratliff and Oldfield [5] and Booth et al. [10], the double adenomas in our case were clearly separated, they were different in that the associated non-ACTH adenoma was relatively large (22 mm in diameter), compressed the normal anterior pituitary gland, and hid the causal tiny ACTH producing microadenoma that was missed preoperatively.

In patients with multiple pituitary adenomas, the treatment outcome may be poor if surgical decision-making is based on the results of preoperative MRI study. According to Hammer et al. [17], 90% of the tumors in patients with Cushing's disease are microadenomas and some are too small (<2 mm) for MRI visualization [18]. In addition, the reported incidence of asymptomatic pituitary tumors ranges from 3–27% [15,19], and recent advances in neuroimaging have resulted in the discovery of unsuspected endocrinologically silent pituitary masses (pituitary incidentalomas) [14,20]. So in order to avoid such a misdiagnosis as our case, the possibility of associated coincidental non-ACTH producing adenomas must be considered in Cushing's disease patients with pituitary macroadenomas [17,18].

Therefore, when only the larger tumor, compressing the surrounding tissue and thereby hiding the presence of another tumor, is misdiagnosed as an ACTH-producing adenoma and removed, the overlooked, co-existing ACTH-producing microadenoma continues to function, as was the case in our patient.

Selective venous sampling, cavernous sinus sampling (CSS) or inferior petrosal sampling, are widely-used techniques for diagnosing of ACTH-producing microadenomas [16,21]. However CSS is recommended only when results of endocrine examinations are atypical for Cushing's disease or any adenomas can not be demonstrated in patients with Cushing syndrome. Therefore CSS should not be recommended for making a differential diagnosis in our case when taking into account that preoperative endocrine data were consistent those of Cushing's disease and an adenoma, although it was macroadenoma, was clearly depicted on MRI.

Watson et al. [22] reported the usefulness of intraoperative ultrasound (IOUS) for the detection of adenomas not visualized on MRI in patients with Cushing' disease. We agree that routine IOUS may be useful for excluding the presence of hidden tumors in these patients.

The possible existence of double adenomas must be considered in the diagnosis of functioning pituitary adenomas and scrupulous examination of preoperative MRI is mandatory in patients with Cushing's disease, especially when macroadenoma is suspected as the causal lesion, because most of Cushing's disease patients present with microadenomas.

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