ECTOPIC pituitary adenoma refers to a condition in which adenomatous pituitary tissue is present outside the sella turcica and is not in continuity with the sellar pituitary gland. Careful radiological, intraoperative, and histological examinations of the relationships among the adenoma, the diaphragma sellae, the pituitary stalk, and the pituitary gland are required to make this diagnosis.

ECTOPIC pituitary adenomas (EPAs) are rare, occurring most often in the sphenoid sinus, suprasellar region, nasopharynx, cavernous sinus, and parasellar areas. In the presence of EPA, the intrasellar pituitary gland tends to be normal or is associated with imaging signs of empty sella syndrome. To our knowledge the presence of EPA associated with CD and intrasellar nonadenomatous pituitary corticotroph hyperplasia has not been reported so far.

Case Report

MUBARAK AL-GAHTANY, M.D., JUAN BILBAO, M.D., KALMAN KOVACS, M.D., PH.D., EVA HORVATH, PH.D., AND HARLEY S. SMYTH, M.D., D.PHIL.

Departments of Neurosurgery and Pathology, St. Michael’s Hospital and University of Toronto, Ontario, Canada

ECTOPIC pituitary adenomas (EPAs) are rare and their association with orthotopic corticotroph hyperplasia has not been published.

The case of a 30-year-old woman with clinical and biochemical evidence of Cushing disease (CD) is reported. A magnetic resonance image obtained preoperatively revealed asymmetrical inhomogeneity of the pituitary gland, which was suggestive of localized adenoma. It also showed what was thought to be a small sphenoid polyp. Postoperatively the latter lesion was found to be an ectopic corticotroph adenoma. The pituitary gland, which was free from any tumor, exhibited diffuse unilateral corticotroph hyperplasia. Clinical, radiological, laboratory, and histopathological findings are presented. A review of the literature and a discussion of possible causes of this unique association between the ectopic corticotroph adenoma and the pituitary hyperplasia are provided.

KEY WORDS • Cushing disease • ectopic adenoma • pituitary hyperplasia • sphenoid sinus

Examination. Investigations revealed a high 24-hour concentration of urinary free cortisol at 11,000 nmol per day (3960 μg/day). The patient’s plasma cortisol level was increased: 1019 nmol/L (36.7 μg/dl) measured in the morning and 614 nmol/L (22.1 μg/dl) in the evening. There was no suppression of cortisol in response to a test of low-dose dexamethasone. No high-dose dexamethasone suppression test was conducted, and the serum concentration of CRH was not measured. A computerized tomography scan of the patient’s abdomen demonstrated normal adrenal glands. Magnetic resonance imaging of the sella turcica with and without Gd enhancement demonstrated a normal pituitary fossa, but an inhomogeneous pituitary gland (Fig. 1 upper). It also disclosed a small globular mass lying along a septum within the left sphenoid sinus; the mass displayed a medium signal intensity on T1-weighted images, which enhanced after injection of Gd (Fig. 1 upper right and lower). The septum itself was deviated to the right side. The lesion was interpreted to be a mucosal polyp.
Inferior petrosal sinus sampling for ACTH showed an IPS/peripheral vein ratio of 3:1, with a right-sided predominance of ACTH response to intravenously administered DDAVP (Table 1).

Operation. Surgery was performed using the transnasal, transsphenoidal approach. A small 3-mm polypoid lesion encountered along the septum in the left sphenoid sinus was excised completely and submitted for pathological examination. The bony sellar floor was intact. It was drilled away and the dura mater was opened. On the right side, the pituitary tissue appeared to be altered with some areas of softening alternating with nodularity. No such abnormality was evident on the left side of the gland. Considering these surgical findings and the preoperative laboratory results, a right hemihypophysectomy was performed together with sampling of the left lobe of the pituitary gland.

Postoperative Course. During the first postoperative 24 hours, the patient’s plasma cortisol level decreased from 484 nmol/L (17.4 μg/dl) in the recovery room to 340 nmol/L at 4 hours, 104 nmol/L at 8 hours, 84 nmol/L at 12 hours, and 79 nmol/L at 16 hours postoperatively (12.2, 3.7, 3, and 2.8 μg/dl, respectively). The patient began to experience generalized asthenia and anorexia, and her blood pressure decreased to 85/50 mm Hg. Fifty milligrams of hydrocortisone sodium succinate (Solucortef) was given intravenously and the patient began a regimen of oral cortisone acetate (37.5 mg daily). She responded well and was released from the hospital on the 3rd postoperative day.

At 6 months postoperatively the patient was experiencing complete disease remission, had lost 15 kg in weight, and her 24-hour urinary free cortisol levels were within the normal range. At 2 years postoperatively complete remission has been maintained.

Microscopic Studies

Tissues were fixed in 10% buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin, PAS, and the Gordon–Sweet silver. Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded sections by using the streptavidin-biotin-peroxidase complex method. Materials for electron microscopy were fixed in 2.5% glutaraldehyde, osmicated, dehydrated in ethanol, and embedded in an Epon–Araldite mixture. No separate fragment of the sphenoid sinus mass was submitted for electron microscopy at the time of surgery because of its small size.
Histological analysis showed that the mass in the left sphenoid sinus was a well-demarcated chromophobic, slightly amphophilic pituitary adenoma underneath the ciliated sinus mucosa (Fig. 2 upper). The adenoma cells exhibited a mild-to-moderate PAS positivity. Immunostaining demonstrated the presence of ACTH and β-endorphin in the cytoplasm of adenoma cells (Fig. 2 center). Immunostaining for CD34 showed that the adenoma was well vascularized.

Immunostaining for growth hormone, prolactin, β-thyroid-stimulating hormone, β–follicle-stimulating hormone, β–luteinizing hormone, the α subunit, S100 protein, neurofilament antigen, chromogranin, glial fibrillary acidic protein, p53, and CRH yielded negative results. Immunostaining was notable for neuron-specific enolase and synaptophysin.

The Gordon–Sweet silver stain demonstrated disruption of the reticulin fiber network (Fig. 2 lower). Histological examination of the right hemihypophysectomy specimen revealed no adenoma.

The Gordon–Sweet silver stain demonstrated disruption of the reticulin fiber network, a characteristic finding in pituitary adenoma (Fig. 2 lower).

Histological examination of the right hemihypophysectomy specimen revealed no adenoma. The most striking alteration was the marked Crooke hyalinization of the corticotrophs, indicating that they were exposed to a glucocorticoid excess, as seen in hypercorticism. Corticotrophs that were positive for PAS and immunoreactive for ACTH and β-endorphin were numerous, and many of them displayed an advanced Crooke hyaline change (Fig. 3 upper). Adenohypophyseal cells immunoreactive for growth hormone, prolactin, β–thyroid-stimulating hormone, β–follicle-stimulating hormone, β–luteinizing hormone, and the α subunit were easily encountered and displayed no abnormalities. The Gordon–Sweet silver stain demonstrated preservation of acini; they were expanded and contained more cells than those found in the normal gland, which was consistent with the diagnosis of hyperplasia (Fig. 3 lower).

With the aid of an electron microscope we observed that the sellar pituitary specimen consisted only of nonadenomatous adenohypophysis and that the specimen displayed an abundance of corticotrophs displaying massive Crooke hyalinization (Fig. 4). Histological examination of the left-lobe biopsy specimen revealed normal pituitary tissue.

Discussion

Ectopic pituitary adenomas are rare. In 185 cases of CD that have been surgically treated by the senior surgical author (H.S.S.), ectopic adenoma has been confirmed in only two: this case and one other reported by Coiré, et al.9 The first reported case of EPA was described by Erdheim in 1909;8,20 since then approximately 50 cases have been reported, including the present one.1,3,6–9,11,13,15–20,22–30,37,39–41,44–54,56–58

The rarity of EPA, despite the frequent presence of ectopic embryonic remnants of the pituitary gland, is intriguing. It is possible that many EPAs are both small and nonfunc-
tation and, thus, are not detected clinically or even during postmortem examination. This notion is supported by the fact that only half of the EPAs reported in the literature have been functioning lesions.

In reported cases of functioning EPAs, CD appears to be the most common pattern of hypersecretion, occurring in 18 of 50 reported cases. Prolactin-secreting adenomas occurred in nine of 50 patients and acromegaly occurred in six. This incidence differs from the reported distribution and frequency of intrasellar adenomas, in which prolactin-secreting adenomas account for 30% of all functioning tumors and ACTH-producing tumors constitute up to 14%.3

One possible explanation of this difference is that ACTH-producing EPAs are more likely to be functioning, thus bringing them to clinical attention and making them appear more prevalent. Pluta46 has suggested that even functioning ACTH-secreting extrapituitary parasellar microadenomas may be more common than reported, because they are treated accidentally and without being diagnosed during the surgical approach to the sella turcica, or during sellar and parasellar radiation treatment, which is used after failure of surgical management.

It is important to entertain the diagnosis of EPA in patients who have typical endocrine syndromes of suspected pituitary origin, but in whom imaging of the sella turcica yields normal findings. This is particularly true in cases of CD, in which ACTH-secreting adenomas too often are difficult or impossible to localize preoperatively because of their small sizes and variable locations.43,57,58 Undisclosed

EPAs may thus be one of the occult reasons why intrasellar exploration may prove nondiagnostic and complete hypophysectomy may fail to correct ACTH hypersecretion in patients with CD.

Histologically, normal adenohypophysis was documented in approximately half of reported cases. In two cases a separate adenoma within the pituitary gland was noted. In the rest of the reported cases normal pituitary glands were indicated by imaging studies or at surgery, or both.

One unique feature of the present case was the coincidental finding of corticotroph hyperplasia in an otherwise normal pituitary gland, adjacent to a histologically verified ACTH-positive ectopic adenoma. There are a number of possible explanations for this unique association. Both the orthotopic pituitary gland and the sphenoidal embryonic remnant may have responded differently to a common influence from the hypothalamus or elsewhere. An excess of CRH could have induced corticotroph hyperplasia in the former while causing adenoma in the latter. This explanation, however, is shadowed by the following: the fact that the serum concentration of CRH was not measured; the good response of CD to surgery, although the presumed source of the CRH and half of the pituitary gland remained untouched; and the findings of unilateral pituitary hyperplasia. It may be possible, however, that the clinical response was due to removing the substantial bulk of the ACTH source, which is usually the adenoma. It may also be possible that it takes CRH some time to produce hyperplastic or adenomatous changes in the rest of the pituitary gland, leading to a clinical recurrence of CD. It has been shown that ACTH-producing cell hyperplasia is more often demonstrable in specimens obtained during total hypophysectomies than from those obtained during partial hypophysectomies and adenomectomies. Thus, the unilateral hyperplasia in the pituitary gland in our case is more than likely a reflection of the limited sampling of the left lobe of the gland. The presence of nodular and asymmetrical hyperplasia in patients with CD, however, has been previously reported.

An alternative explanation of this coexistence is that the ectopic tumor might be the source of the CRH, which in turn induced corticotroph hyperplasia in the nearby pituitary gland. This mechanism would have provided a perfectly logical explanation for selling corticotroph hyperplasia in this case, but immunohistochemical staining of the ectopic adenoma cells for CRH proved negative. Although staining for CRH was repeated twice by applying different antibodies, it is still possible that the CRH in the tumor cells was not reactive to the antibodies that were used. Access of tumor-produced CRH into the pituitary gland can be provided either through systemic circulation, which makes one think that this would lead to generalized pituitary hyperplasia, or directly through venous channels existing between the sphenoid sinus and the pituitary fossa, which, based on its microvascular anatomy, may lead to unilateral hyperplasia in the pituitary lobe adjacent to the ectopic tumor. Presence of such vascular connections has been offered previously as an explanation of ongoing pituitary function, despite ostensibly complete hypophysectomy, because ectopic pituitary tissue may remain a functional part of the hypothalamic–adenohypophysial system, by virtue of transsphenoidal vascular connections.

Fig. 4. Electron micrograph showing massive accumulation of cytokeratin filaments (Crooke hyaline) in the hyperplastic corticotrophs (stars). Original magnification x 5300.

M. Al-Gahtany, et al.
Ectopic corticotroph adenoma of the sphenoid sinus

The ability of the tumor to secrete CRH and the presence of the means to transport and distribute this CRH to the pituitary gland seem to be the minimum requirements for the coexistence of pituitary hyperplasia and an ACTH-positive adenoma according to the present theory. Thus, the rarity of a typical intrapituitary ACTH-secreting adenoma associated with pituitary hyperplasia in the rest of the gland may be due, in part, to the lack of excretion of both CRH and ACTH by the tumor cells and, in part, because of the arrangement of the hypophysial portal system, which does not allow the product of the pituitary cells to circulate within the gland but rather to be carried away to the systemic circulation.

Coexistence of a pituitary adenoma and pituitary hyperplasia, however, has been reported. A higher incidence of this coexistence has been found in patients with multiple endocrine neoplasia syndrome Type 1. Hyperplasia of ACTH-producing cells is more often demonstrable in specimens obtained during total hypophysectomies than in those obtained during partial hypophysectomies and adenomectomies, and recurrences of adenomas are more frequent in pituitary glands in which there is perianatomous ACTH-producing cell hyperplasia. Cook and McCarthy reported two cases in which there was evidence of corticotroph hyperplasia in specimens obtained during total hypophysectomy performed after removal of a pituitary adenoma failed to cure the patient’s symptoms of CD. Cushing syndrome persisted in both patients after the hypophysectomies, but subsequently was cured by pituitary irradiation. These two cases support the argument that the association of corticotroph hyperplasia and ACTH-positive adenoma may be more common than reported, but is not identified because total hypophysectomies are not usually performed in the presence of a pituitary adenoma. Although ectopic adenomas were not identified in these cases, the failure of a response to total hypophysectomy and the subsequent response to irradiation raise the possibility of an ectopic adenoma that is responsible for ACTH production and, perhaps, even CRH production causing corticotroph hyperplasia. Saeger has demonstrated that nodular ACTH-producing cell hyperplasia is frequently found apart from ACTH-producing tumors in CD and Nelson syndrome, and on this basis he has suggested that the adenomas in both diseases arise from hyperplasia. Alternatively, it may be possible that tumor-produced CRH was the cause of the hyperplasia.

Inferior petrosal sinus sampling in this case indicated an IPS/peripheral vein ACTH ratio of 3:1 with a right-sided predominance. This led to the decision to perform a right hemihypophysectomy and sampling of the left lobe.

The ACTH lateralization was possibly caused by the corticotroph hyperplasia present on the right side, an asymmetry that was corroborated preoperatively on MR images and intraoperatively by microsurgical inspection. Whether the EPA contributed to the elevated central/peripheral ACTH ratio is unknown. It is possible, however, that venous drainage from the ectopic tumor reached the IPS through venous drainage of the sphenoid sinus. The reported diagnostic accuracy of inferior petrosal sinus sampling over imaging for localization of pituitary pathology in patients with Cushing’s disease yielded a negative result.


duction of CRH. Even a right–left IPS gradient of ACTH may fail to lateralize the adenoma correctly in up to 20 to 50% of cases. This case and those reported by Pluta further illustrate the necessity of caution in interpreting the results of IPS sampling and provide another possible explanation for the discordance observed between findings of MR images and IPS sampling studies.

Conclusions

Ectopic pituitary adenomas are rare. They are found in places in which embryonic remnants of the Rathke pouch or misplaced cells from the pars tuberalis are located, the most common of which is the sphenoidal sinus.

Pituitary corticotrophic hyperplasia associated with EPA has not been described previously. Although the exact mechanism of this association is not known, possible explanations have been discussed in this paper.

Ectopic pituitary adenoma should be kept in mind in all patients with persistent CD in whom sellar imaging studies appear normal and in whom previous surgical exploration

References


J. Neurosurg. / Volume 98 / April, 2003

895