Ectopic Adrenocorticotropic Hormone–Secreting Pituitary Adenomas: An Underestimated Entity

**BACKGROUND:** The diagnosis of Cushing disease is based on endocrinological parameters, with no single test being specific. In some patients, dynamic thin-slice sellar magnetic resonance imaging fails to detect a pituitary tumor.

**OBJECTIVE:** The purpose of this study is to investigate the role of ectopic pituitary adenoma in this situation.

**METHODS:** In a retrospective chart review, 5 patients (6%) with ectopic adenomas were identified in 83 consecutive patients undergoing transsphenoidal surgery for adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas by 1 surgeon.

**RESULTS:** In all 5 patients (all female, 32-41 years of age), an exclusively extrasellar ACTH-secreting adenoma was excised. Three adenomas were located in the cavernous sinus, 1 in the sphenoid sinus, and 1 in the ethmoidal cells. Histologically, none of the tumors showed signs of aggressiveness. Three of the 5 adenomas specifically expressed somatostatin receptor 5. In 4 patients with Cushing disease, postoperative remission was obtained, with 1 recurrence after 14 months. In the patient with Nelson syndrome, ACTH decreased from 800 to 80 pg/mL. Three patients underwent previous surgery elsewhere, including 1 hypophysectomy. In this case, the ectopic adenoma (positive for somatostatin receptor 5) in the ethmoidal cells turned out to be positive on gallium 68 DOTATATE positron emission tomography/computed tomography.

**CONCLUSIONS:** The incidence of primarily ectopic ACTH-secreting adenomas in this series was 6%. In cases of negative MRI findings, an ectopic ACTH-secreting adenoma should be taken into account. 68Ga DOTATATE positron emission tomography/computed tomography may identify ectopic pituitary adenomas. Hypophysectomy should always be avoided in primary surgery for CD.

**KEY WORDS:** Cushing disease, Ectopic Cushing syndrome, Pituitary adenoma, Pituitary surgery, Somatostatin receptor

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adenomas by 1 neurosurgeon between December 2001 and June 2015, 5 (6%) patients were identified who retrospectively (3 recurrent procedures) or primarily (2 primary procedures) presented with primary ectopic (extrásellar) adenomas: 4 patients with CD and 1 with Nelson syndrome. This retrospective chart review focused on the preoperative data. Because the preoperative workup was performed by different endocrinologists, assessments, not specific numerical values, are given in Table 1. All patients underwent microsurgical transsphenoidal pituitary surgery combined with neuronavigation and, since 2006, the use of intraoperative direct contact ultrasound (iUS). Postoperatively, all patients with CD were kept in the intermediate care unit without substitution of glucocorticoids. Serum cortisol levels were determined every 4 hours until secondary hypocortisolism occurred. This was taken as an early sign of endocrinological remission.9,10 The mean follow-up after indicator surgery was 41 months (range, 18-62 months; median, 42 months).

A histological workup of all surgical specimens was done according to a protocol published previously.11 Immunohistochemistry for somatostatin receptors (SSTRs) was performed with antibodies for SSTR2a, SSTR5 (Zytomed, Berlin, Germany), and SSTR3 (Schulz, Jena, Germany). The data are given in Table 2.

RESULTS

Patient 1

A 32-year-old female patient had Cushing syndrome for 7 years and endocrinologically proven CD (Table 1), negative findings on sellar MRI, and positive IPSS results (44-fold centroperipheral gradient for ACTH). The first transsphenoidal exploration, done elsewhere, was negative surgically and histologically, and hypercortisolism persisted. The medial wall of any cavernous sinus (CS) was not opened, according to the surgical records. Postoperative sellar MRI was suspicious for a left intrasellar microadenoma (Figure 1). During MRI-navigated and iUS-assisted resurgery (indicator operation), no tumor was identified in the sellar cavity (histologically proven scar on the left side). Because of the MRI findings, the intact medial wall of the left CS was opened and a purely intracavernous ACTH-positive microadenoma was excised, which was histologically proven (densely granulated, Ki-67 <1%, SSTR negative). The postoperative decrease in serum cortisol was slow (third postoperative day), and a low-dose dexamethasone suppression test revealed normal suppression. Remission of clinical signs subsequently developed. There was a recurrence of hypercortisolism after 14 months. Another sellar MRI was negative. Without endocrinological deficits at this time, the patient opted for a bilateral adrenalectomy instead of radiation therapy to the left CS. Follow-up (62 months after repeat surgery, 44 months after bilateral adrenalectomy) revealed increasing plasma-ACTH. However, development of Nelson syndrome has not yet occurred.

Patient 2

This 36-year-old woman presented with weight gain, hair loss, and fatigue for 1 year. Endocrinologically, atypical CD or ectopic ACTH secretion was suspected, with negative MRI findings and lack of response to corticotropin-releasing hormone (CRH) during IPSS. Baseline levels of central ACTH (left side) were elevated 6-fold compared with peripheral ACTH level (Table 1). Another thin-slice dynamic sellar MRI (1.5 T) did not reveal any findings for the sellar compartment itself. T2-weighted coronal images showed an extension of the gland to the left CS. Using iUS and MRI navigation, a 5-mm microadenoma located outside the sellar compartment in the left CS was removed. The medial wall of CS was not infiltrated and was intact before resection (Figure 2). The complete left pole of the gland was resected and histologically tumor free and did not adhere to the sellar covering. The specimen from the left CS histologically showed a densely granulated pituitary adenoma strongly expressing ACTH. Expression of Ki-67 was <1% of nuclei. Expression of p53 was negative. SSTR5 was specifically positive (located at the cell membranes) (Table 2). Secondary hypocortisolism occurred within 1 day, and long-term remission was achieved without persisting endocrinological deficit. Substitution of hydrocortisone was ceased after 5 months. Symptom-free follow-up after surgery is currently 55 months.

Patient 3

Thirteen years earlier, a 21-year-old woman presented with typical CD (Table 1) and underwent extensive (negative) transsphenoidal external and internal pituitary (sellar) exploration by a very experienced pituitary surgeon elsewhere, without remission of hypercortisolism. According to the detailed surgical report, the medial wall of the CS was not opened. Bilateral

<table>
<thead>
<tr>
<th>TABLE 1. Endocrinological and Radiological Data Before Any Pituitary Operation in the Current Series</th>
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<tr>
<td><strong>Baseline Levels</strong></td>
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<tr>
<td>Patient 1: F, 32 y</td>
</tr>
<tr>
<td>Patient 2: F, 36 y</td>
</tr>
<tr>
<td>Patient 3: F, 34 y</td>
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<tr>
<td>Patient 4: F, 38 y</td>
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<tr>
<td>Patient 5: F, 41 y</td>
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A, ACTH, adrenocorticotropic hormone; Co, morning level of serum cortisol; CPG, centroperipheral ACTH-gradient; CRHT, corticotropin-releasing hormone stimulation test; CS, cavernous sinus; f, female; ldDXM, high-dose dexamethasone suppression test; IPSS, inferior petrosal sinus sampling; ldDXM, low-dose dexamethasone suppression test; ND, not done; NS, not stated; PS, paranasal sinus; UFC, urine free cortisol/24 h; ↑, elevated or stimulated; ↑↑, highly elevated or stimulated; (↑), slightly elevated; ↔, normal or no reaction; ↓, diminished or suppression; (↓), slightly diminished; (+), positive finding; (?), primarily quoted as questionable/nonspecific finding.
adrenalectomy was performed 4 years later. Plasma ACTH increased over years, and MRI finally revealed an intracavernous macroadenoma (maximal diameter of 21 mm) on the left side when the patient was 34 years of age. During iUS-assisted, MRI-navigated transsphenoidal reoperation, a purely intracavernous tumor was removed and histologically proven (densely granulated, 2% Ki-67). The tumor tissue showed cytoplasmic (non-specific) expression of SSTR5. The medial wall of the left CS was intact, although medially dislocated (Figure 3). The pituitary gland had no connection to the intracavernous tumor and did not adhere to the medial wall of the CS. Postoperatively, plasma ACTH decreased from 800 pg/mL to 80 pg/mL (normal morning level: 64 pg/mL). After surgery, a VI nerve palsy on the left side was present, which completely resolved within 6 months. During follow-up (42 months), no tumor remnants could be identified on repeated MRI scans.

Patient 4

This 38-year-old woman presented with weight gain and arterial hypertension within 1.5 years. Endocrinological findings revealed typical CD, with loss of diurnal rhythm of serum cortisol, elevation of 24-hour urinary free cortisol (4-fold), increased plasma ACTH, partial suppression of cortisol and ACTH after 8 mg dexamethasone, and slight stimulation after CRH. Sellar MRI was negative for an intrasellar microadenoma. However, a small intrasphenoid mass was noted on MRI and CT (Figure 4A–4C), which was read as a mucosal adenoid. During iUS-assisted and MRI-navigated extensive external and partially internal pituitary exploration (biopsy on the right side), the small extrasellar reddish mucosal tumor, which appeared like a vascular lesion (no frozen section was performed intraoperatively), was removed with the midline septum of the sphenoid sinus (Figure 4D and 4E). Histologically, this turned out to be a sparsely granulated pituitary adenoma expressing ACTH, and Ki-67 was 1% to 2% (Figure 4F–4I). SSTR5 was strongly and specifically positive at the tumor cell membranes. The pituitary biopsy specimen showed Crooke cells but no tumor tissue. Hypocortisolism developed within 1 day. Remission was achieved without other endocrinological deficits, and substitution with hydrocortisone was tapered and ceased after 18 months. Postsurgical follow-up is 26 months at present.

Patient 5

This female patient (age 41 years) presented with symptoms of hypercortisolism for 6 months. ACTH-dependent hypercortisolism

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Granulation</th>
<th>ACTH +, %</th>
<th>Other Hormone</th>
<th>Ki-67/Mib-1, %</th>
<th>p53</th>
<th>SSTR</th>
<th>Crooke Cells in Anterior Lobe</th>
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<tr>
<td>Patient 1</td>
<td>CS</td>
<td>Dense</td>
<td>20/30/40</td>
<td>None</td>
<td>&lt;1</td>
<td>0</td>
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<td>SSTR3(+) SSTR5 ++</td>
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<tr>
<td>Patient 3</td>
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<td>Dense</td>
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<td>2</td>
<td>0</td>
<td>SSTR5(+) NA</td>
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<td>Patient 4</td>
<td>PS</td>
<td>Sparse</td>
<td>20/40/40</td>
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<td>&lt;1%</td>
<td>SSTR2a(+) SSTR3(+) SSTR5 ++ ++</td>
</tr>
<tr>
<td>Patient 5</td>
<td>PS</td>
<td>Sparse</td>
<td>0/0/5</td>
<td>None</td>
<td>&lt;1</td>
<td>0</td>
<td>SSTR3(+) SSTR5 ++</td>
</tr>
</tbody>
</table>

*ACTH, adrenocorticotropic hormone; CS, cavernous sinus; NA, not applicable; PS, paranasal sinus; SSTR, somatostatin receptor. Expression of ACTH: percentage of cells with weak/medium/strong expression; reaction to Mib-1 and p53: percentage of nuclei; SSTR: specific reaction ++ (strong), ++ (moderate), and + (weak); nonspecific (cytoplasmic) reaction: (+).
was proven; however, functional tests were equivocal: a high-dose dexamethasone test showed suppression of serum cortisol, but there was no increase in cortisol with CRH application. Because sellar MRI was negative, IPSS was performed, and a centero peripheral gradient for ACTH (3-fold after CRH) was found. Transsphenoidal microsurgical exploration was performed elsewhere, and the findings were negative. Hypercortisolism persisted. Gallium 65 (68Ga) DOTATATE positron emission tomography/computed tomography (PET/CT) showed a suspicious finding in the colon (subsequent colonoscopy findings were negative) and some enhancement in the anterior skull base. The latter was rated as nonspecific by the radiologists and not communicated to the endocrinologist (Figure 5). With the diagnosis of an occult CRH source, hypophysectomy was performed. Hypercortisolism persisted, however, and bilateral adrenalectomy was suggested. The patient was referred for a second opinion. In retrospect, a small mass in the posterior ethmoidal cells on the left side was visible and unchanged in all available MRI and CT scans (Figure 5). CT revealed a bony defect of the skull base (Figure 5). Because of the suspicion of an ectopic adenoma or a CRH-secreting tumor, eg, a gangliocytoma (postulating some functioning rest of the anterior pituitary lobe), an MRI-navigated transnasal reexploration (indicator operation) was performed. An adenoma was excised from the posterior ethmoidal cells on the left side with intraoperative cerebrospinal fluid leakage and histologically proven (sparsely granulated, 5% ACTH-positive cells, both antibodies negative for CRH, Ki-67 <1%). SSTR5 turned out to be weakly positive at the tumor cell membranes (specific), SSTR2a was negative, and SSTR3 was weakly positive in the cytoplasm (nonspecific). Postoperative serum cortisol rapidly decreased to subnormal levels. Follow-up after reoperation is 18 months.

DISCUSSION

Purely extrasellar (ectopic) ACTH-secreting pituitary adenomas are a rare source of CD. In this study, only patients were included in whom contamination with tumor tissue due to previous operations was ruled out (eg, intracavernous tumor remnant after partial resection of an intra-/extrasellar adenoma or intrasphenoidal tumor metastasis after a previous transsphenoidal approach).

Incidence and Site

Over the past 2 years, 3 reviews of the literature, each in the context of a single case, have been published.2,12,13 In conclusion, 1 group collected 21 ectopic adenomas in the sphenoid sinus,
including 2 of their own surgical series, whereas others reviewed 8 cases with tumors in the sphenoid sinus or paranasal cavities, 5 tumors in the CS, and 1 adenoma located in the suprasellar space. Another overview reported 18 adenomas within the sphenoid sinus (counting the case of Flitsch et al7 twice), and 23 tumors outside the sphenoid sinus, with 10 adenomas located in 1 CS or the suprasellar space. In conclusion, even in centers with a large case load, the appearance of or the perception of the presence of an ectopic ACTH-secreting adenoma in CD appears to be low. The only series of ectopic ACTH-secreting adenomas presented to date identified 5 patients of a surgical series of 626 patients.14 However, the rate of 5 of 83 consecutive patients with CD reported here (6%) may suggest that a closer view of their cases, and particularly those who underwent negative pituitary exploration, might reveal a higher rate of ectopic adenomas by other authors as well.15 According to the current literature, the remission rate in CD should be >90% for microadenomas10,16,17 and may even approach 100% if early recurrent surgeries after failure of the first surgery are included and the possibility of ectopic ACTH-secreting adenoma is kept in mind by the surgeon.9,18

Preoperative Testing and Imaging

Sellar MRI can be negative in CD in as many as 40% of cases. Moreover, a second, non-ACTH-secreting adenoma may be present and lead the surgeon to resect a nonfunctional lesion at a first attempt.5,10 The diagnosis of CD and the specification of CD is based on endocrinological evaluation only.19-21 If those are contradictory, IPSS is performed to prove the hypophysal origin of ACTH oversecretion.8,22,23 Johnston et al13 reported that, from preoperative endocrinological data, no conclusion regarding a possible ectopic ACTH-secreting adenoma in the sphenoid sinus can be drawn: in 10 of 12 reported cases, cortisol decreased >50% during a high-dose dexamethasone test; in 3 of 9 cases, ACTH increased >50% after administration of CRH; and in 8 of 9 patients, IPSS revealed a central-to-peripheral ACTH gradient. This is consistent with the data found in our 5 patients with ectopic ACTH-secreting adenomas (Table 1). In our series, it is remarkable that not only patients with tumors in the CS but also in the ethmoidal cells had a clear-cut central-to-peripheral ACTH gradient during IPSS. This elucidates the significance of venous drainage of the skull base and across the midline when interpreting IPSS results. Lateralization of ACTH hypersecretion may be especially unreliable.22

SSTR and PET/CT

We performed detection of somatostatin receptors 2a, 3, and 5 in our 5 patients, demonstrating specific (membrane-bound) reaction to SSTR5 in 3 tumors. The somatostatin receptors were currently reviewed,24 and SSTR5 has been identified as the most common somatostatin receptor in ACTH-secreting pituitary

**FIGURE 3. Patient 3. A-D, the adenoma (arrows) is visible in the left cavernous sinus (coronal T1-weighted magnetic resonance images after gadolinium enhancement from anterior to posterior), which is ballooned by the tumor (C and D). The medial wall of the left cavernous sinus can be anticipated (dark line medial to the tumor), and the pituitary remnant is visible (C).**
adenomas,25 which is in accordance with our results. The physiological distribution of 68Ga DOTATATE has been investigated by PET/CT and revealed a significant uptake in the pituitary gland.26-28 This effect was mainly attributed to the expression of SSTR2.26 Remnants of pituitary adenomas showed less uptake than residual pituitary gland.29 This could imply that an intrasellar microadenoma can be missed by this technique because of pituitary uptake. A first case of an ectopic ACTH-secreting pituitary adenoma positive on 68Ga DOTATATE PET/CT was previously reported.30 Our second, although primarily missed, case in the current series (immunohistochemically specifically positive only for SSTR5) and the positive histological detection of SSTR5 in 3 of our 5 patients make it reasonable to perform 68Ga DOTATATE PET/CT in cases of CD with negative sellar MRI in the future.

Operative Outcome

iUS can detect intrapituitary microadenomas in 69% to 77% of cases, even if preoperative MRI findings were negative, and can therefore prevent extensive internal exploration of the gland.9,31 However, localization of an ectopic ACTH-secreting adenoma is the first challenge. If anticipated, removal of adenomas from the paranasal cavities is straightforward and yields good results.7,12,13 Resection is challenging in case the tumor site is within the CS, which includes the risk of vascular damage and cranial nerve...
The latter was temporarily seen in 1 of our 3 patients with a purely intracavernous adenoma. The introduction of magnetic resonance navigation and iUS offers the opportunity to open the CS safely and to dissect close to the intracavernous internal carotid artery. However, intracavernous extension of pituitary adenomas remains the main cause of incomplete tumor removal with persistence or recurrence of hypercortisolism. Development of ectopic adenomas in the sphenoid sinus and other paranasal cavities might well be explained by remnants of the azygous (median) Rathke pouch. This appears not to be the case for exclusively parasellar tumors with an intact medial wall of the CS; failed separation of the primary pituitary gland resulting in sellar and pharyngeal glands may explain ectopic adenomas in the paranasal sinuses, and ectopic “overshoot” migration may cause suprasellar adenomas. The reason, however, why most of the reported ectopic pituitary adenomas are ACTH positive remains obscure. The adenomas in the current series were not atypical or aggressive, even not in case of Nelson syndrome (patient 3). Intracytoplasmic granulation differed between the 3 tumors in the CS (dense) and the other 2 tumors in the paranasal area (sparse). The granulation pattern has been proven relevant for growth hormone–secreting adenomas. In addition to the different mechanism of emergence of the ectopic site of the adenomas, this could be another clue to the presumption that ectopic adenomas in the CS may be a distinguished entity. Compared with other pituitary adenomas, ACTH-secreting adenomas have a different profile of expression of proteases, such as metalloproteinases (matrix metalloproteinase -2 and -9),
their inhibitors (tissue inhibitor of metalloproteinase-2), and the receptor of urokinase (urokinase-type plasminogen receptor), which might explain the tendency of these adenomas to infiltrate the medial wall of the CS despite their small size. However, this does not explain the exclusive dislocation of a whole adenoma to another dural compartment. The medial wall of the CS is not immunohistochemically different from other dural structures; it shows thin areas but no apertures. Human fetal walls of the CS mainly are composed of type III collagen and are of weak histological structure, which could be a reason for early displacement of pituitary cells. The development of the peripituitary envelope from paired (lateral) mesenchymal structures seems to be complete during the 13th week of gestation, whereas the developing anterior lobe of the gland in part already wraps around the posterior lobe in the seventh and eighth weeks. ACTH-producing cells prematurely differentiated within the Rathke pouch when both transcription factors Hes1 and Prop1 were lost, leading to downregulation of N-cadherin and thus enabling ACTH-producing cells to form ectopic foci outside the Rathke pouch. In the future, new insights into genetic characteristics of ACTH-secreting pituitary adenomas might be interesting regarding the development of ectopic displacement.

CONCLUSION

The evolution of ACTH-secreting pituitary adenomas located exclusively in the CS remains obscure. There is no specific pattern of endocrinological data pointing to ectopic ACTH-secreting adenomas. MRI in CD may be misleading or negative, and it is always nonspecific. In cases with negative findings on MRI and/or pituitary exploration, the presence of ectopic ACTH-secreting adenomas should be taken into account, as these may be more frequent than previously thought. Ga DOTATATE PET/CT may be helpful in the identification of ectopic adenomas and deserves further evaluation. Hypophysectomy should be avoided in primary surgery.

Disclosures

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**Acknowledgment**

Dedicated to Dieter K. Lüdecke, MD, master of pituitary surgery, admired teacher, and friend.