
CASE REPORT

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LOCATION OF ECTOPIC ADRENOCORTICAL HORMONE-SECRETING TUMORS CAUSING CUSHING'S SYNDROME IN THE PARANASAL SINUSES

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Abstract: *Background.* The majority of ectopic adrenocorticotrophic hormone (ACTH)-secreting tumors are localized in the chest or abdomen. Occasionally, these tumors are found in the paranasal sinuses.

Methods. We present 2 unusual cases of ectopic ACTH syndrome whose ACTH-secreting tumors were localized in the paranasal sinuses and describe their biochemical and radiological presentation.

Results. The first patient had an ACTH-secreting olfactory neuroblastoma originating in the ethmoid sinuses. The second patient had a clinical course and biochemical findings indistinguishable from pituitary ACTH-dependent Cushing's syndrome, except for negative petrosal sinus sampling. Head imaging showed a "polyp" in the left maxillary sinus-secreting ACTH. Both patients went into remission following surgical resection and recovered normal pituitary-adrenal axis function.

Conclusion. Ectopic ACTH secretion may originate from lesions in the paranasal sinuses. This accessible location allows for direct immunohistochemical diagnosis with ACTH staining. Surgical resection/radiation therapy can result in complete remission of the disease and restoration of normal pituitary-adrenal function. ©2008 Wiley Periodicals, Inc. *Head Neck* 31: 699–706, 2009

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Ectopic ACTH-secreting tumors are the second most common etiology of Cushing's syndrome, after ACTH-secreting pituitary adenomas.¹ In their typical presentation, and in contrast to pituitary adenomas, they show rapid development of symptoms, fewer manifestations of cortisol excess, frequent manifestations of mineralocorticoid excess, weight loss, and hyperpigmentation.² Some ACTH-secreting bronchial carcinoid tumors, however, can remain occult for years and the clinical manifestations develop gradually.³ The diagnostic challenge is the localization of the tumor. The usual location is the chest^{2,4} and the most frequent pathology a bronchial carcinoid responsible for about 30% of cases. Less frequent pathologies are thymic carcinoids,⁵ pancreatic islet cell tumors,⁶ pheochromocytomas,⁷ paragangliomas,⁸ and medullary thyroid carcinomas.⁹ Based on these reported sites, the search usually include CT or MRI of the chest, abdomen and pelvis,

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octreotide radionuclide scans, and selective venous sampling for ACTH gradients. Octreotide scans are sensitive for identifying somatostatin receptor-expressing tumors, but they are not helpful when these receptors are not present.¹⁰ Selective venous sampling procedures, although occasionally useful, may overlook small gradients in ACTH secretion.¹¹ We report 2 cases of ectopic ACTH-secreting tumors located in the paranasal sinuses, highlighting the importance of including these structures in the search for these tumors.

CASE REPORTS

Case 1. A 48-year-old man was seen with a 3-week history of progressive malaise, leg edema, blurred vision, and muscle weakness. He was severely hypokalemic (serum potassium-2.1 mOsm/L) and had metabolic alkalosis. He had noted facial swelling and hyperpigmentation for several months before his admission. History was significant for “chronic sinus congestion” treated with nasal polypectomy 2 years earlier. His weight had been stable and his blood pressure was normal. On physical examination, his blood pressure was 140/70 mm Hg; he had a hyponasal voice, left lower lung crackles, bilateral axillary lymphadenopathy, 1+ pitting edema, and onychomycosis in his toenails. He had decreased proximal muscle strength. Abnormal laboratory studies included white count 16,000/mm³ (4000–10,000) with 93% neutrophils (36–75), serum potassium (2.2 [3.5–5]) and CO₂ (40 mOsm/L [22–34]), calcium 7 mg/dL (8.6–10.3), phosphorus 1.8 mg/dL (2.7–4.6), parathyroid hormone (PTH) 153 pg/mL (12–75), 25-hydroxy vitamin D < 6 ng/mL (25–80), and serum albumin 2.4 g/dL (3.5–4.9). Radiographic examination of the chest revealed minimal left pleural effusion and faint nodular opacity over the anterior portion of the second left rib consistent with callus surrounding an old fracture as demonstrated in a subsequent CT scan. The scan also showed osteopenic-appearing vertebral bodies, 2 small benign-appearing lung nodules, and bilateral nodular enlargement of the adrenal glands. The adrenal findings led to the measurement of plasma cortisol of 123.5 µg/dL (7–22), ACTH 648 pg/mL (5–52), and urine-free cortisol of 11,640 µg/day (20–90). The clinical picture was consistent with ectopic ACTH-dependent Cushing’s syndrome (hyperpigmentation, volume overload, severe hypokalemia, and leukocytosis), and it was supported by the very high cortisol levels. For

temporary control, ketoconazole was given in doses of up to 1 g/day, along with potassium supplements. Cortisol was decreased, symptoms were improved, and hypokalemia was corrected. A search for an ectopic ACTH-secreting tumor included CT of the abdomen and pelvis, which were negative. A pituitary MRI was obtained to rule out an atypical ACTH-secreting adenoma. Although the pituitary gland was normal, a multilobular mass with scattered strong enhancement was found centered in the ethmoid paranasal sinuses and extending into the frontal and maxillary sinuses, while the sphenoid sinus was spared. The mass protruded through the cribriform plate to the right of midline, pushing the inferior aspect of the frontal lobe superiorly. The intracranial portion measured 1.8 × 1 cm, whereas the mass in the paranasal sinuses measured 5 × 9 × 6 cm. Abnormal enhancement along the inferior frontal gyrus was suspicious for subarachnoid spread. The lesion did not involve the orbits, but a mucous opacity was noted in the maxillary sinuses (Figure 1A). Studies were carried out to characterize this mass.

To confirm the association of the paranasal mass with ectopic ACTH secretion, a biopsy from the nasal cavity portion was performed and demonstrated nested architecture of small round blue cells with uniform mildly pleomorphism forming rosettes (Figure 1C) and positive cytoplasmic staining for ACTH (Figure 1D). Because the results unequivocally uncovered the source of ACTH excess, further biochemical diagnostic procedures, that is, corticotropin-releasing hormone (CRH) stimulation test or 8-mg dexamethasone suppression, were not obtained. To search for metastases, an Indium-111 octreotide scan (6 mCi) was performed, identifying positive tracer localization in the area of the paranasal sinus tumor (Figure 1B). There were no other focal areas of increased radiotracer uptake. An abundance of tumor cells were positive for synaptophysin, S-100 protein, chromogranin A, and tyrosinase. The pathology was consistent with an olfactory neuroblastoma (also known as esthesioneuroblastoma). The tumor was surgically exposed via a frontal approach and a gross total resection was accomplished. ACTH levels following surgery decreased (26 pg/mL) but were not completely suppressed as it would be expected with complete tumor resection. The patient recovered from surgery and subsequently received adjuvant radiotherapy. Follow-up over the next 9 months showed normalization of ACTH and cortisol levels and

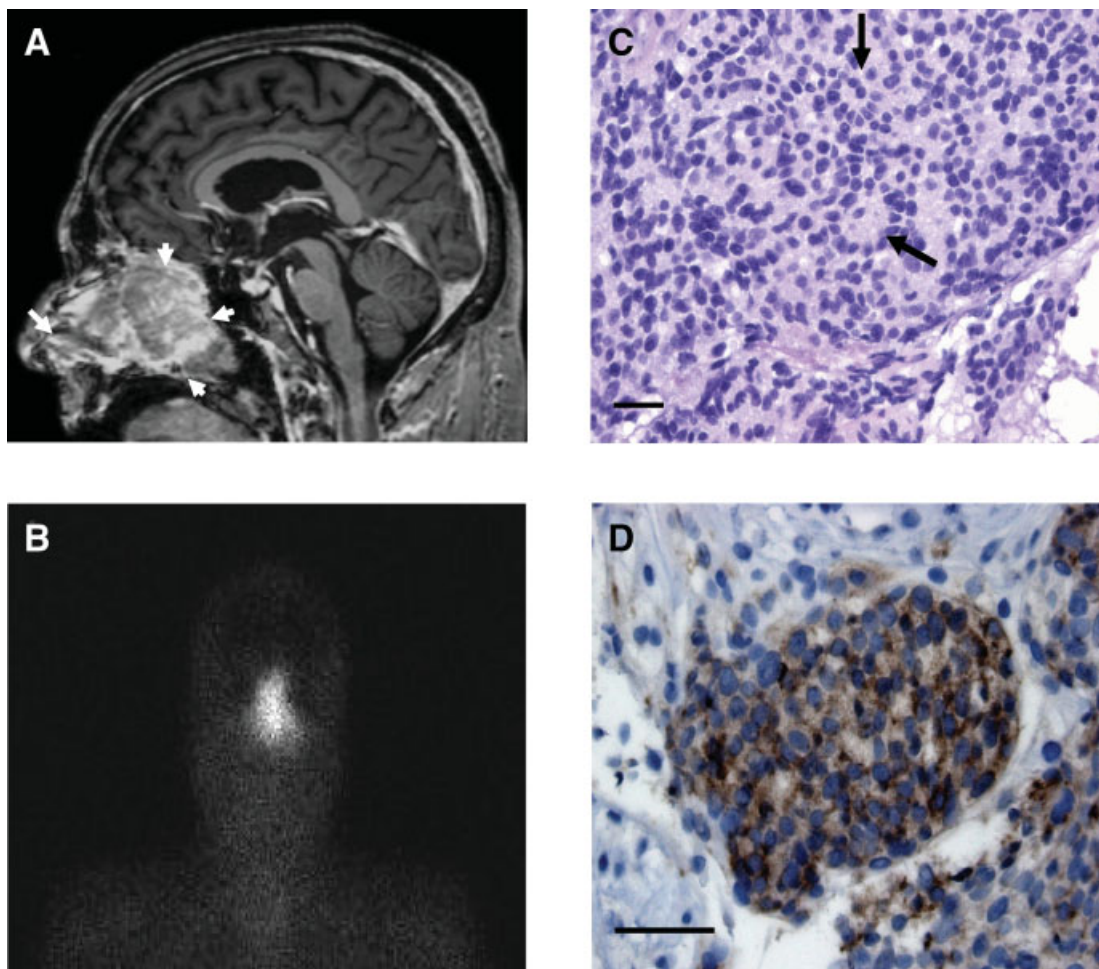


FIGURE 1. (A) Case 1 midsagittal MRI view, displaying a multilobular mass (white arrows) in the ethmoid and maxillary paranasal sinuses, whereas the sphenoid sinus is spared. The mass protrudes through the cribriform plate to the anterior cranial fossa. Arrows outline the tumor borders. (B) Frontal view of Indium-111 octreotide scan, identifying positive tracer localization in the area of the paranasal sinuses (white arrow). (C) Hematoxylin-eosin staining of case 1 paranasal sinus tumor biopsy, demonstrating small round blue cells with mild pleomorphism forming rosettes (black arrows). (D) Immunoperoxidase (brown) conjugated anti-ACTH antibody immunohistochemistry, showing positive cytoplasmic staining for ACTH (bars = 50 μ m).

complete suppression (ACTH, <5 pg/mL; cortisol, 1.7 mcg/dL) after 1 mg dexamethasone.

Case 2. A 30-year-old woman was seen with a 3½-year history of a 45-lb weight gain and purple abdominal striae following pregnancy. She noted facial fullness, dry skin, acne, easy bruising, hypertension, fatigue, amenorrhea, cramps in her hands and feet, facial hirsutism, nocturia, and occasional ankle edema. She also noted decreased libido, increased irritability, mood swings, intermittent crying spells, depression, insomnia, short attention span, and occasional decreased memory. She complained of right groin pain when bearing weight or moving her leg. She was gravida-II, para-II, and had a history of impaired glucose tol-

erance during her pregnancy. Physical examination revealed truncal obesity, facial fullness, prominent supraclavicular fullness and buffalo hump, skin atrophy, pale purple striae in the abdomen and thighs, hyperpigmentation of the knuckles of both hands, acanthosis nigricans in her neck, tinea versicolor over the neck and lower back, areas of ecchymosis in her lower extremities and warts in her fingers. Abnormal laboratory studies included a white count of 11,000/mm³, and serum electrolytes were normal. A bone scan to investigate her hip pain showed a stress fracture of the right femoral neck. She subsequently fractured her right hip and required open reduction with internal fixation and capsulorrhaphy. Her clinical presentation and physical findings were

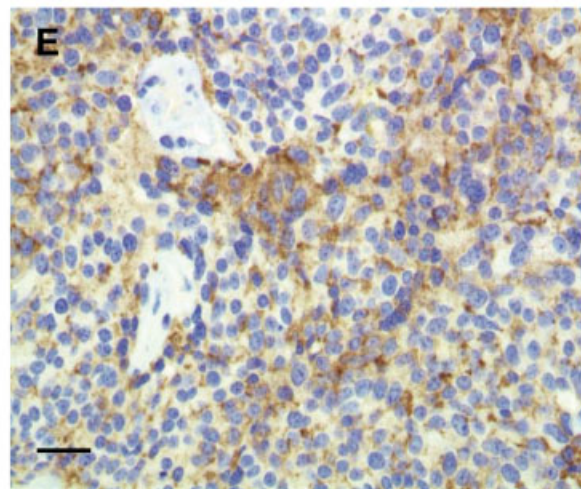
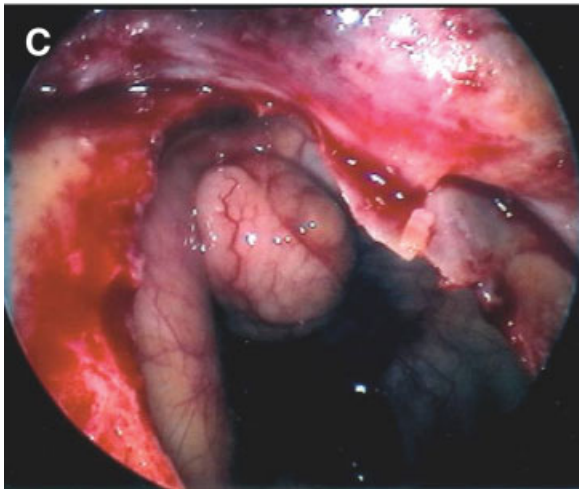
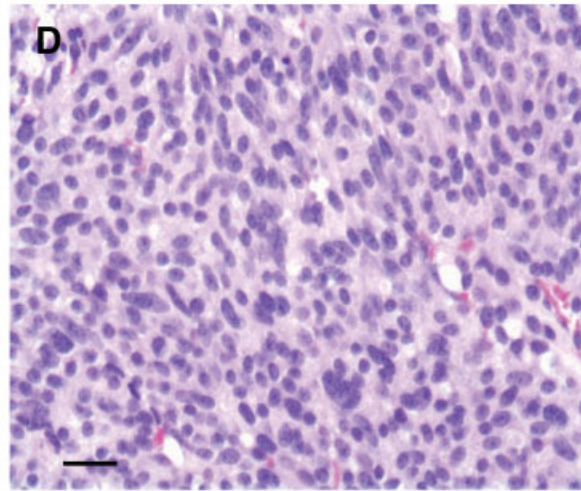
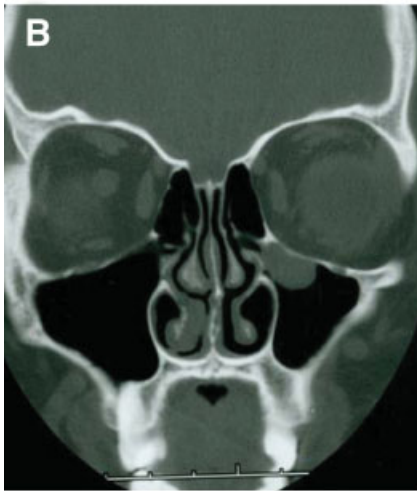
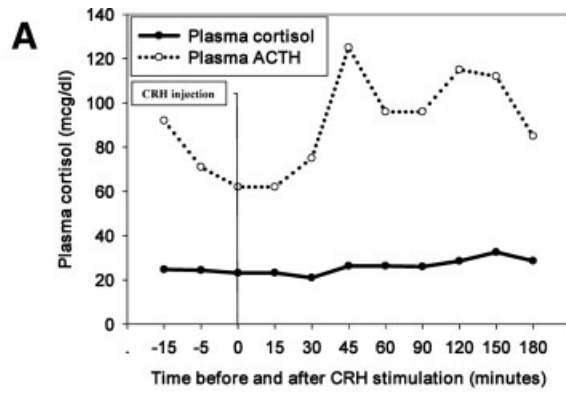


FIGURE 2. Case 2. (A) Corticotropin-releasing hormone (CRH) stimulation test, demonstrating a small adrenocorticotropic hormone (ACTH) response to CRH. (B) CT scan of paranasal sinuses, showing a left maxillary mass. (C) Gross appearance of the sinus mass during endoscopic resection. (D) Hematoxylin-eosin staining of case 2 maxillary sinus tumor biopsy, demonstrating small round blue cells. (E) Immunoperoxidase (brown) conjugated anti-ACTH antibody immunohistochemistry, showing positive cytoplasmic staining for ACTH (bars = 50 μ m).

Table 1. Unstimulated petrosal sinus catheterization and sampling demonstrating the lack of ACTH gradient between petrosal sinuses and peripheral venous blood, suggesting ectopic ACTH secretion.

| Sample | Plasma ACTH levels, pg/mL | | |
|--------|---------------------------|-------|------------|
| | Left | Right | Peripheral |
| I | 38 | 42 | 44 |
| II | 39 | 47 | 40 |
| III | 54 | 56 | 72 |
| IV | 45 | 47 | 50 |

Abbreviations: ACTH, adrenocorticotropic hormone.; U17OHC, urinary 17-hydroxycorticosteroids; CRH=corticotropin releasing hormone; Units: cortisol, mcg/dl.

consistent with ACTH-dependent Cushing's syndrome, which was confirmed by elevated urine free cortisol (624 mcg/24 hours) and nonsuppressed ACTH (60 pg/mL). Two milligrams of dexamethasone suppression test failed to achieve cortisol suppression, whereas 8-mg dexamethasone suppression test lowered both cortisol (36 to 10 mcg/dL) and ACTH (40 to 16 pg/mL), suggestive of pituitary ACTH-dependent Cushing's syndrome. This clinical picture was supported by a CRH stimulation test (Figure 2A) that stimulated ACTH secretion. In contrast, pituitary MRI was negative and chest and abdominal CT were also negative.

Inferior petrosal sinus catheterization showed no ACTH gradient between petrosal sinus and peripheral venous blood, suggesting ectopic ACTH secretion (Table 1). Systemic venous catheterization showed a marked step-up in ACTH levels in the left internal jugular and left angular vein (Table 2). A CT scan of the paranasal sinuses showed a 1-cm mass apposed to the superomedial wall of the left maxillary antrum (Figure 2B). This mass was interpreted as a possible benign polyp or mucous retention cyst. Because the result of the venous sampling suggested the ACTH step-up was in the vein draining the mass, and the patient underwent endoscopic resection of this mass (Figure 2C). The pathology was consistent with a neuroendocrine tumor (Figure 2D). Immunohistochemistry was positive for ACTH (Figure 2E). Following tumor resection, ACTH levels were completely suppressed, and the patient underwent remission of her Cushing's syndrome. A 3-year follow-up showed that the patient had regained normal pituitary-adrenal function.

Methods. Urinary-free cortisol and serum cortisol were determined by radioimmunoassay using

the Diagnostic Products Corporation kits and plasma ACTH by the Allegro radioimmunoassay. MRI was performed using a Tesla-1.5 magnet. Dexamethasone suppression tests were performed with a low dose (0.5 mg every 6 hours for 8 doses) followed by a high dose (2 mg every 6 hours for 8 doses). For CRH stimulation, 1 mcg/kg of CRH was administered intravenously after obtaining baseline samples; blood samples were then obtained every 15 minutes for the first hour and every 30 minutes for the next 2 hours. Inferior petrosal sinus catheterization and sampling were carried out under local anesthesia by inserting catheters into each of the femoral veins at the groin. Samples for ACTH were obtained simultaneously from each inferior petrosal sinus and a peripheral vein. Systemic venous sampling was carried out by placing a catheter at different levels in the venous system under fluoroscopic visualization. Specifically, samples were obtained from the left angular vein. Because the systemic venous sampling followed the inferior petrosal sinus sampling, only 4 sets of baseline samples drawn 5 minute apart were obtained, and CRH was not injected to blur peripheral ACTH differences. ACTH expression by tumor was confirmed by immunohistochemistry using formalin-fixed paraffin-embedded 5-mm sections. For case number 1, an anti-ACTH rabbit polyclonal antibody (DAKO, Carpinteria, CA; catalog no. A0571) was used at 1:2000 dilution with no antigen retrieval. Detection of primary antibody was performed using the avidin-biotin peroxidase method and 3,3'-diaminobenzidine (DAB) as a chromogen. For case number 2, an anti-ACTH rabbit polyclonal antibody (Ventana Medical Systems, Tuscon, AZ; catalog no. 760-2506) was used as a prediluted antibody with CC1 standard pretreatment (pH-8.0 for 60 minutes). Detection of primary antibody

Table 2. Systemic venous catheterization and sampling showing a marked ACTH step-up in the left internal jugular and left angular vein.

| Sampling site | ACTH, pg/mL |
|----------------------------|-------------|
| SVC | 214 |
| Left mid-innominate | 199 |
| Left high-internal jugular | 348 |
| Left mid-internal jugular | 464 |
| Left low-internal jugular | 536 |
| Left angular vein | 2880 |
| Peripheral × 8 sites | 111-117 |

Abbreviation: ACTH, adrenocorticotropic hormone; SVC, superior vena cava.

was performed using the avidin–biotin peroxidase method and DAB as a chromogen. For cell markers, the following antibodies were used: for S100, antibodies from Dako-Cytomation at a 1/250 dilution; for CGA antibodies from Ventana Medical Systems, and for tyrosinase, antibodies from Novocastra at a 1/10 dilution. The study was approved by the institutional review board for Human Experimentation, and patients gave written informed consent.

DISCUSSION

We report 2 cases of Cushing's syndrome secondary to ectopic-ACTH secretion in which the neoplasm-secreting ACTH was located in the paranasal sinuses. This is a location not usually recognized and may lead to failure of localization and eventual adrenalectomy for resolution of the hypercortisolemia. In case 1, the patient lacked overt symptoms of hypercortisolemia, possibly because of the relatively rapid progression of the disease. However, subtle symptoms may have been present for a longer time but ignored by the patient. For example, presenting hypocalcemia and vitamin-D deficiency was likely a result of Cushing's syndrome^{12,13} and strict vegetarian diet. His complaints of "nasal stuffiness and sinus problems" were attributed to a prior diagnosis of nasal polyps and sinusitis. Case 2 presented with a more indolent course, and both her clinical presentation and biochemical findings were suggestive of pituitary ACTH-dependent disease. However, the negative pituitary MRI and inferior petrosal sinus catheterization suggested an ectopic ACTH source. Although not a common location for ectopic ACTH syndrome, there are, as we illustrate here, ACTH-secreting tumors that originate from the paranasal sinuses. Other reported cephalic pathologies as a cause of Cushing's syndrome are ectopic pituitary adenomas. These adenomas derive from normal pituitary tissue arrested outside the sella turcica in the course of normal embryonic development¹⁴ and as a remnant of the Rathke's pouch developmental tract. These clusters of cells are uniformly embedded in the mucoperiosteum and most commonly located in the sphenoid bone. Although initially regarded as an endocrine inactive tissue, it is now recognized that these clusters are composed of a diversity of normal pituitary cells^{15,16} and have the capacity to develop a vascular network during the fourth decade and establish endocrine communication with the hypothalamus.¹⁷ Abnormal prolif-

eration and excessive secretion of pituitary hormones by these rhinopharyngeal pituitary tissues may be evoked by molecular events that lead to neoplastic development. Although these rhinopharyngeal pituitary tissues can be found in the normal population, reports of functioning ectopic pituitary adenomas are uncommon and their presentation quite variable. They may behave like ACTH-secreting pituitary adenomas, respond to suppression with dexamethasone, and because of their proximity to the pituitary gland petrosal sinus sampling, give confusing results suggesting a pituitary source. Alternatively, they may not exhibit the classical dynamic profile of a pituitary adenoma. Schteingart et al¹⁸ reported a patient with ectopic ACTH syndrome produced by an adenoma in the mucosa of the sphenoid tissue. This patient had a clinical presentation consistent with pituitary adenoma but failed to respond to metyrapone and high-dose dexamethasone, suggesting an ectopic etiology. Kammer et al¹⁹ reported a patient with ACTH-dependent Cushing's syndrome who suppressed on the high-dose dexamethasone test, but pituitary imaging was negative. A combination of radiation therapy to the pituitary combined with aminoglutethamide and metyrapone failed to achieve a sustained remission. Following bilateral adrenalectomy, there was continued rise of ACTH and expansion of a previously ill-defined sphenoid sinus tissue. Resection of this tissue revealed a chromophobe adenoma. Suzuki et al²⁰ reported another case of ectopic pituitary adenoma in the sphenoid sinus who presented with subtle symptoms of Cushing's syndrome for more than a year, resistant to low-dose dexamethasone suppression test and CRH stimulation. Radiographic evidence of a tumor mass in the sphenoid sinus helped localize the source of ACTH. Although the majority of the cases involve the sphenoid sinus, others occupy the cavernous sinus²¹ and other suprasellar regions.²² The other types of ectopic ACTH-secreting tumors originating in the paranasal sinuses are much less frequent but may behave aggressively. Case 2, in this report, behaved both clinically and on dynamic testing like a pituitary adenoma, and only the negative pituitary MRI and inferior petrosal sinus catheterization led to the search for a nonpituitary ACTH source.

ACTH-secreting olfactory neuroblastomas have been described only 3 times in the past. One was a case of ACTH-dependent Cushing's syndrome that failed to stimulate with CRH or suppress with a high dose of dexamethasone. This

patient presented with florid Cushing's syndrome along with hypertension and severe hypokalemia. Petrosal sinus sampling was positive for an ACTH step-up, but the pituitary MRI was negative. The patient responded to metyrapone, but repeated imaging after 10 months identified an olfactory neuroblastoma in the ethmoid sinus. The tumor was surgically excised and treated with adjuvant radiation therapy, but it reappeared in the maxillary sinus and was finally fully resected. Arnesen et al²⁴ reported a patient presenting with florid Cushing's syndrome who had a "nasal polyp" consistent with an olfactory neuroblastoma that immunostained positive for ACTH. Yu et al²⁵ reported a patient with florid Cushing's syndrome with negative body cross-sectional imaging studies. An ACTH-secreting olfactory neuroblastoma extending to the cranium was identified by both positive emission tomography and octreotide scan. Hypercortisolemia was initially controlled by metyrapone and external beam radiation.

Although ACTH-secreting olfactory neuroblastomas are extremely rare, nonsecreting tumors are also uncommon. Thus far, only 1000 cases have been described who, like case 1, presented mainly with nasal congestion.²⁶ The prognosis of these malignant tumors is relatively poor with a 5-year survival rate of 45% to 70%.²⁷ The treatment approach consists of extensive resection and radiation therapy, followed by resection of recurrent disease. The recurrence rate is high and tends to involve the maxillary sinuses and neck lymph nodes and may occur after a decade.^{28,29} The previous 2 cases of ACTH-secreting olfactory neuroblastoma had a favorable outcome of at least 5 years, probably because the clinical manifestations of Cushing's syndrome led to an earlier diagnosis and treatment. It is also possible that the ability to synthesize and secrete ACTH required a more differentiated and less aggressive tumor biology.^{23,24} Other rare paranasal and cranial ACTH-secreting neuroendocrine tumors,^{30–32} as well as 1 case of ACTH-secreting nasopharyngeal carcinoma³³ and meningioma,³⁴ have been described.

In summary, we present 2 cases of ectopic ACTH syndrome, in which the source of ACTH was in the paranasal sinuses. The cases illustrate the variegated clinical phenotype of the syndrome, ranging from the classical description with rapid onset and progression, minimal manifestations of hypercortisolism, high ACTH and cortisol levels, and pronounced hypokalemia to the more indolent clinical course, which resembles clinically and biochemically classical pituitary ACTH-

dependent disease. Case 1 followed the first pattern, whereas case 2 illustrates the latter. Given a patient with ACTH-dependent Cushing's syndrome, the following findings should prompt a more careful investigation for paranasal location of an ectopic ACTH source: (1) a normal pituitary MRI, (2) negative or inconclusive inferior petrosal sinus catheterization, (3) negative imaging of the chest and abdomen, and (4) symptoms or imaging findings of paranasal pathology.

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