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Case Report

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Ectopic ACTH-Secreting Pituitary Adenoma of the Maxillary Sinus: A Rare Cause of Cushing's Syndrome

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Abstract

We describe a rare case of Cushing's syndrome caused by an ectopic adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma located in the maxillary sinus and outline the diagnostic and therapeutic challenges. A 41-year-old woman presented with an eight-year history of progressive weight gain, fatigue, type 2 diabetes mellitus, and hypertension, leading to a diagnosis of Cushing's syndrome. Inferior petrosal sinus sampling confirmed an ectopic ACTH source. Fluorodeoxyglucose-positron emission tomography demonstrated a 12-mm lesion in the right maxillary sinus, which was successfully removed via an endonasal approach. Postoperatively, cortisol levels normalized and her symptoms resolved. The patient remains in remission 2.5 years following surgery. This case highlights the importance of considering ectopic ACTH-secreting adenomas in patients with Cushing's syndrome without a sellar mass and emphasizes the need for thorough diagnostic evaluation to ensure accurate tumor localization and optimal surgical management.

Keywords: Cushing's syndrome, adrenocorticotropic hormone (ACTH), pituitary neoplasms, paranasal sinuses, maxillary sinus, endoscopic sinus surgery

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Introduction

Ectopic pituitary adenomas are exceedingly rare benign neoplasms of pituitary origin that arise outside the sella turcica, without any involvement of the sellar region (1). These tumors are frequently misdiagnosed as other neuroendocrine or epithelial neoplasms that may arise in similar anatomical locations. The current literature on ectopic pituitary adenomas is limited to isolated case reports and small case series, which collectively highlight the heterogeneous presentation of these lesions in terms of anatomical location, radiological features, and biochemical functionality. This variability often complicates timely diagnosis and management.

The majority of patients with adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome (CS) have an ACTH-secreting pituitary adenoma located within the sella turcica. However, prolonged investigation reveals an ectopic ACTH-secreting pituitary adenoma situated along the embryological migratory path of Rathke's pouch in exceedingly rare instances. Despite the suggestion of surgery as the first-line treatment in these cases, evidence to guide long-term management, surveillance, and recurrence prediction remains limited.

To our knowledge, only a small number of ectopic pituitary adenomas located in the maxillary sinus have been reported (2). Here, we report a patient with a longstanding history of Cushingoid features, whose workup revealed an ectopic ACTH-secreting pituitary adenoma in the right maxillary sinus. This case underscores the diagnostic and therapeutic challenges posed by these rare tumors and contributes to the growing body of literature aimed at guiding their management.

Case Presentation

A 41-year-old woman with an eight-year history of progressive weight gain, fatigue, type 2 diabetes mellitus, and hypertension was referred to the endocrine clinic. She had no other significant past medical history and had previously been told that her symptoms were consistent with fibromyalgia. She had undertaken research on the internet and had noted several fibromyalgia forums referencing CS. She felt her symptoms and physical features were consistent with this diagnosis. She had no history of exogenous steroid use and no cause for physiological hypercortisolism. Clinical assessment confirmed signs consistent with CS (facial plethora, obesity, dorsocervical fat pad, proximal myopathy, and hirsutism). A review of old photographs demonstrated a marked change in the patient's physical appearance over the preceding five years.

Initial diagnostic investigations confirmed CS. A non-suppressed ACTH level of 39.1 ng/L confirmed ACTH-dependent CS (Table 1). Concurrent findings of secondary hypothyroidism initially suggested a pituitary source. Subsequently, she underwent corticotropin-releasing hormone stimulation testing, which yielded indeterminate results for a pituitary source. A contrast-enhanced magnetic resonance imaging (MRI) of the pituitary gland revealed a possible right-sided microadenoma (Figure 1a). She was discussed at the regional pituitary multidisciplinary team (MDT) meeting and inferior petrosal sinus sampling (IPSS) was recommended. IPSS favored an ectopic rather than pituitary source of ACTH. Based on these findings, she underwent cross-sectional imaging. A computed tomography (CT) scan of her neck/thorax/abdomen and pelvis was unremarkable. Fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging revealed a 12-mm right maxillary sinus lesion with avid tracer uptake (SUV_{max} 11.9) (Figure 1b). There were no areas of FDG tracer uptake in the brain or pituitary gland.

Following biochemical confirmation of CS, she was prescribed prophylactic low molecular weight heparin (enoxaparin 40 mg once daily). In view of escalating hyperglycemia (HbA1c 108 mmol/mol) and in anticipation of surgery, she was commenced on the maximum tolerated dose of metyrapone (500 mg twice daily). Dose adjustments were guided by regular early morning serum cortisol assessment (target mean 150-300 nmol/L) (3). Her diabetes was managed with basal-bolus insulin therapy (insulin glargine U-300 and insulin aspart) and metformin 1 g twice daily. Her hypertension was treated with two agents (lisinopril 20 mg once daily and amlodipine 10 mg once daily). She was referred to the ear, nose and throat MDT meeting and following a CT (Figure 1c), which confirmed the lesion's presence, the decision was made to proceed with surgery. She underwent endonasal resection of the lesion from the right anterior maxillary sinus wall using a pre-lacrimal approach. Through the nasal cavity, an incision was made anterior to the inferior turbinate along the lateral nasal wall. The mucosa was elevated, and the medial wall of the maxillary sinus was drilled anterior to the nasolacrimal duct, creating a wide surgical window into the maxillary sinus. This approach provided direct access to the anterior, lateral, and inferior walls of the maxillary sinus while preserving the lacrimal drainage system. After complete excision of the lesion, the mucosal flap was repositioned.

Table 1. Laboratory test results

Test	Result	Reference range
24-hour urinary free cortisol (1)	934 nmol/24 hrs	<120 nmol/24hrs
24-hour urinary free cortisol (2)	906 nmol/24 hrs	<120 nmol/24hrs
Overnight dexamethasone suppression test	221 nmol/L	Suppression expected
ACTH	39.1 ng/L	
TSH	1.68 mIU/L	
Free T4	8.2 pmol/L	12-22 pmol/L
CRH stimulation test (ACTH)	24.1 to 86.5 ng/L	>50% increase
CRH stimulation test (cortisol)	783 to 806 nmol/L	>20% increase
IPSS (central-to-peripheral ratio pre-CRH)	<2	
IPSS (central-to-peripheral ratio post-CRH)	<3	
IPSS (prolactin-normalized ratio)	0.4	

CRH: Corticotropin-releasing hormone, IPSS: Inferior petrosal sinus sampling, TSH: Tiroid stimulating hormone, ACTH: Adrenocorticotropic hormone

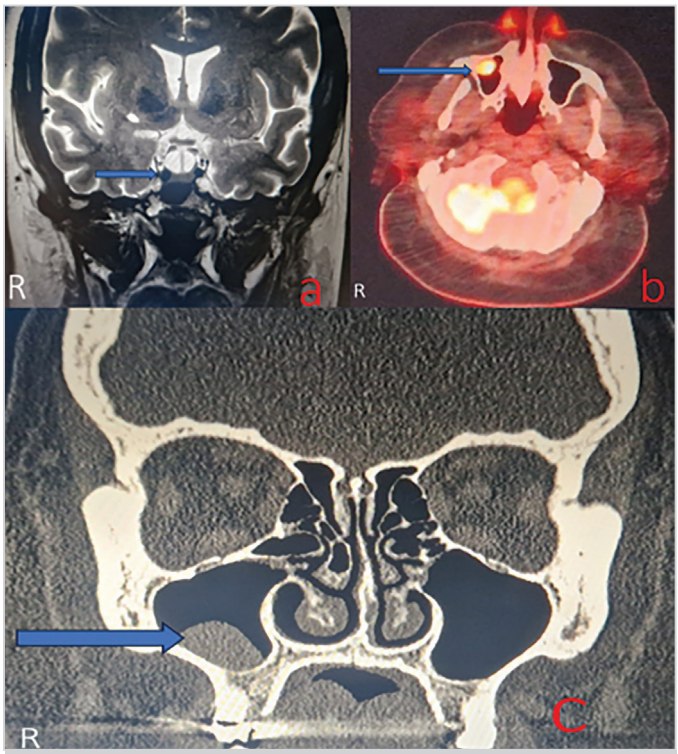

Figure 1. a) Coronal MRI of the pituitary with gadolinium shows a partially empty sella and a small non-enhancing focus in the right anterior pituitary (blue arrow), **b)** The blue arrow highlights a rounded polypoid lesion arising from the anterior wall of the right maxillary antrum, demonstrating marked FDG uptake (SUV_{max} 11.9), **c)** Coronal CT reveals a well-defined low-density lesion at the base of the right maxillary antrum (blue arrow)
MRI: Magnetic resonance imaging, FDG: Fluorodeoxyglucose, CT: Computed tomography

Macroscopic examination revealed a 28×20×8 mm tumor arising from the right maxillary sinus. Histological examination demonstrated respiratory-type sinonasal mucosa infiltrated by a pituitary adenoma (Figure 2). No cytologic atypia or evidence of tumor apoplexy was identified. Immunohistochemical analysis showed diffuse positivity for ACTH, synaptophysin, chromogranin, and TPIT, confirming the diagnosis of a corticotroph adenoma. The Ki-67 proliferation index was low (<1%), indicating low proliferative activity. An independent second histopathological review confirmed the diagnosis of an ectopic ACTH-secreting pituitary adenoma (ectopic corticotropinoma).

A 9 a.m. serum cortisol level of 34 nmol/L on the first postoperative day was consistent with early biochemical remission. Hydrocortisone replacement therapy was initiated at a dose of 10 mg on waking, 5 mg at lunchtime, and 5 mg in the afternoon. At 2.5-year follow-up, she remains in clinical and biochemical remission. Antihypertensive therapy has been discontinued, and she no longer requires glucose-lowering medication. A recent HbA1c of 38 mmol/mol is consistent with sustained diabetes remission. She has also lost 20 kg since surgery.

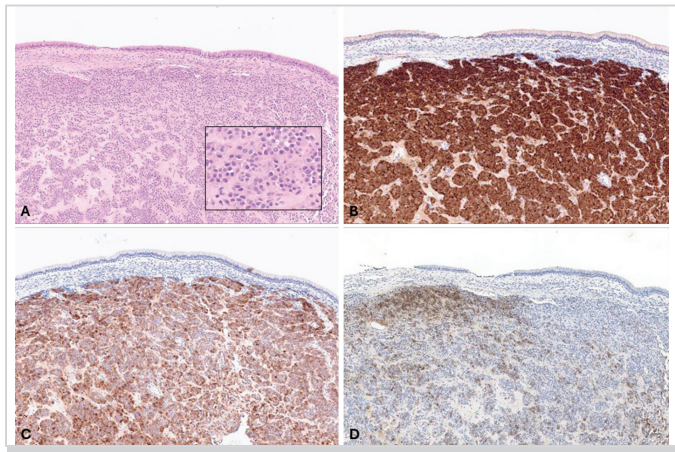

Figure 2. Histopathological images. **A)** H&E shows sinonasal mucosa lined by respiratory epithelium. The lamina propria contains small tumor cells arranged in sheets, nests, and trabeculae. The tumor cells have pale amphophilic cytoplasm and small nuclei (insert). Insert: ×400 magnification, **B)** Synaptophysin is strongly positive, **C)** Chromogranin is also positive, **D)** ACTH shows patchy positivity, **A-D)** ×50 magnification
H&E: Hematoxylin and eosin, ACTH: Adrenocorticotropic hormone

The patient provided written informed consent for the publication of clinical details and images.

Discussion

Pituitary adenomas are among the most common intracranial tumors, typically benign and confined to the sella turcica. Approximately 15% of these tumors secrete ACTH, giving rise to the clinical picture of CS (4). In contrast, ectopic pituitary adenomas arising outside the sella are exceptionally rare, with only a small number of cases reported in the literature. The published cases reveal marked variability in clinical presentation, imaging features, and hormone secretion profiles (5). Unusual sites for ectopic pituitary adenomas include the ethmoid sinus, the temporal bone, the nasal bridge, Meckel's cave and even the thalamus (6).

Ectopic pituitary adenomas originate from the remnants of normal pituitary tissue derived from Rathke's pouch during embryological development. They are most commonly found along this migratory pathway, in regions such as the sphenoid sinus, the suprasellar region, the clivus, the cavernous sinus, and the nasopharynx (2). Zhu et al. (7) reported that among 180 patients with ectopic pituitary adenomas, the most common locations were the sphenoid sinus (34.4%) and the suprasellar region (25.6%), followed by the clivus (15.6%), the cavernous sinus (13.3%) and the nasopharynx (5.6%). These lesions can also establish vascular supply and endocrine communication with the hypothalamus. Although the exact

factors influencing their location and development remain unclear, the presence of an ectopic pituitary adenoma in the maxillary sinus—as seen in this case—is notably atypical, lying well off this midline migratory route and distinct from the ethmoid sinus, temporal bone, nasal bridge, Meckel's cave, and thalamus reported as other rare, non-midline sites.

The clinical presentation of ectopic pituitary adenomas often correlates with their anatomical location. Patients with suprasellar ectopic pituitary adenomas are more likely to present with menstrual disorders and visual changes, while those with clival ectopic pituitary adenomas are more likely to suffer from headaches (7). The diverse locations and non-specific symptoms of ectopic pituitary adenomas make their diagnosis challenging, often leading to misdiagnosis and delayed treatment.

Several case reports of ectopic pituitary adenoma located within or adjacent to the maxillary sinus have been described in the literature. Sindoni et al. (6) describe a 49-year-old man with ACTH-dependent CS who underwent further imaging following an unsuccessful surgical attempt to resect a presumed pituitary adenoma. An 18F-choline PET/CT scan demonstrated avid uptake in a nodule within the left maxillary sinus. Subsequent transnasal endoscopic resection and histological analysis confirmed the diagnosis of an ectopic ACTH-secreting pituitary adenoma. Both our case and the one reported by Sindoni et al. (6) presented with ACTH-dependent CS and were successfully treated with surgical resection. However, our case utilized FDG-PET for localization, while Sindoni et al. (6) used 18F-choline PET/CT. This highlights the utility of different imaging modalities in localizing these rare tumors. Additionally, both patients achieved biochemical remission following surgical resection, demonstrating the effectiveness of surgery as the primary treatment modality for these rare tumors.

Our case highlights the diagnostic challenges involved in the work-up of CS and underscores the importance of a thorough, stepwise approach to investigating patients with hypercortisolemia. Ectopic pituitary adenomas are rare and diverse in location and presentation; they may frequently be overlooked in the differential diagnosis of CS. Campana et al. (5) describe an apparent higher prevalence of clinically functioning ectopic pituitary adenomas when compared to sellar-located pituitary adenomas. On review of the literature, positive staining for ACTH was described in 36% of cases, 13% of which were clinically silent. Given that ectopic pituitary adenomas are often misdiagnosed, it is essential to screen any patient presenting with hypercortisolemia and no clear source for the possibility of an ectopic pituitary adenoma. The presence of a pituitary adenoma within the sella turcica should not exclude the consideration of an ectopic pituitary adenoma, especially if the biochemical findings are discordant.

Surgical removal is the treatment of choice for ectopic pituitary adenomas and allows further evaluation of the roof of the sinus to guide any additional management (8). The use of various medical therapies has been described, including dopamine agonists for prolactin secreting ectopic pituitary tumors (9). However, these treatments are non-curative and are likely to result in re-growth once stopped. The use of radiotherapy both as an initial treatment and post-operatively has also been reported (8). Often such adjuvant therapy was recommended because of an incorrect initial diagnosis and brings with it similar risks seen with radiation to the pituitary fossa.

The dilemma in a rare case such as this is the natural history of the tumor following surgical resection both in terms of tumor growth and/or recurrence. In the case series reported by Thompson et al. (8), 29 of 32 patients with sphenoid sinus ectopic pituitary adenomas had available follow-up data. The average follow-up duration was 10.2 years post-surgical resection. Four patients had recurrence or persistence of the tumor after surgery. Two of these patients were given adjuvant radiotherapy and are now disease free. Seltzer et al. (10) also suggest favorable outcomes with the possibility of long-term remission from CS for functional ectopic pituitary adenomas resected from the sphenoid sinus. Given their rarity, however, no formal evidence-based treatment pathways exist for the investigation and management of ectopic pituitary adenomas. This is particularly the case for a tumor located away from the midline and anatomically distant from the pituitary gland.

Correct localization of an ectopic pituitary adenoma in this case to the maxillary sinus, ensured the patient did not undergo unnecessary investigation or treatment. Given the increased mortality associated with CS even after successful treatment, the case highlights the need for prompt tumor identification to reduce a patient's long-term exposure to hypercortisolemia. Our patient remains in biochemical remission 2.5 years post-surgery and as a result has benefited from improvements in blood pressure and glycemic control. However, the potential for recurrence in this very rare case is largely unknown. In the absence of any long-term surveillance data in the literature, we will need to assess the extent to which that strategy is appropriate, having opted for biochemical surveillance. We hope this will help better inform future clinicians in how to manage these rare tumors.

Conclusion

This case underscores the diagnostic and therapeutic challenges posed by ectopic pituitary adenomas, particularly those located outside the typical embryological migratory path, such as within the maxillary sinus. This underscores the importance of maintaining a broad differential diagnosis in patients with ACTH-dependent CS who have discordant

imaging and biochemical findings, even when an apparent sellar lesion is present. Accurate localization in this case prevented unnecessary treatments and led to successful surgical resection, with the patient achieving biochemical remission and clinical improvement. However, the long-term behavior of such rare tumors remains uncertain. In the absence of established guidelines, careful biochemical surveillance and case reporting will be essential to improving future recognition, management strategies, and outcomes for patients with ectopic pituitary adenomas.

Ethics

Informed Consent: The patient provided written informed consent for the publication of clinical details and images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.W., K.L., W.B., Design: G.W., Data Collection and/or Processing: T.K., K.L., T.B., Analysis or Interpretation: T.K., K.L., W.B., Literature Search: G.W., T.K. Writing: G.W., T.K.

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Main Points

- Cushing's syndrome is commonly caused by an adrenocorticotropic hormone secreting pituitary adenoma. In very rare cases, the pituitary gland can be separate from the sellar turcica and ectopically located.
- Ectopic pituitary adenomas are most commonly found in areas linked to the development of the pituitary gland such as the midline sinuses.
- Any patient presenting with hypercortisolemia and no clear source should be screened for an ectopic pituitary adenoma.
- Surgery is the first line treatment for ectopic pituitary adenomas with favorable outcomes reported in the literature.

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