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Ectopic Acromegaly Arising from a Pituitary Adenoma within the Bony Intersphenoid Septum of a Patient with Empty Sella Syndrome

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Abstract

Objective To describe the work-up and treatment of rare ectopic acromegaly caused by a biopsy-proven somatotroph pituitary adenoma located within the bony intersphenoid septum of a patient with empty sella syndrome (ESS).

Methods We report the presentation, clinical course, diagnostic work-up, and lesion localization and treatment challenges encountered in a 55-year-old patient, with a brief review of relevant literature.

Results A 55-year-old African-American man presented with acromegaly and ESS. Attempts to definitively localize the causative tumor were unsuccessful, though petrosal sinus sampling supported central growth hormone production and imaging suggested bone-enclosed subsellar pituitary tissue. Endoscopic endonasal transphenoidal exploration was undertaken with resection of a somatotroph pituitary microadenoma, and subsequent clinical improvement and biochemical remission. Retrospective review revealed the patient's pituitary to have been located ectopically within a unique bony intersphenoid septum.

Conclusion This report describes the first known case of an ectopic pituitary adenoma located within the midline bony intersphenoid septum, which we postulate to have resulted from anomalous embryological pituitary migration. Intra-intersphenoid septal tumors should be considered in cases of apparent central acromegaly with ESS or absence of tumor tissue within the paranasal sinuses or other peripheral locations.

Indexing Acromegaly, ESS, pituitary adenoma, sphenoid sinus septum.

Keywords

- ▶ acromegaly
- ▶ empty sella syndrome
- ▶ pituitary adenoma
- ▶ sphenoid sinus septum

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Background

Empty sella syndrome (ESS) describes a cerebrospinal-fluid-filled sella turcica associated with a shrunken and/or flattened pituitary gland. Pituitary function is generally preserved, though hyperprolactinemia or partial-to-total hypopituitarism occurs in approximately 50% of patients.¹⁻³ The most prevalent hormone deficiency in this syndrome is growth hormone (GH) deficiency, affecting 35 to 61% of adult patients with ESS.⁴⁻⁶ Pituitary *hyper*function only rarely occurs in ESS, and acromegaly is perhaps the least common manifestation in this setting.⁷⁻⁹

While autoremission of acromegaly after pituitary infarction or hemorrhage has been described, it is uncommon for an acromegaly-causative pituitary adenoma to evade visualization on pituitary magnetic resonance imaging (MRI), much less for an empty sella (ES) alone to be present.^{10,11} In cases where only an ES is visualized, ectopic acromegaly should be considered, though it is responsible for less than 1% of cases. The vast majority of ectopic acromegaly results from neuroendocrine GH releasing hormone (GHRH)-secreting tumors, but isolated reports have described ectopic acromegaly from GH-secreting pancreatic islet-cell or lymphoma neoplasms,^{12,13} and 14 cases have been ascribed to abnormally located pituitary tissue.¹⁴

This case describes the work-up and treatment of a phenomenon not previously documented—rare ectopic acromegaly caused by a biopsy-proven somatotroph pituitary adenoma located within the bony intersphenoid septum of a patient with baseline ESS.

Clinical Case

A 55-year-old African-American man presented with a history of having grown “bigger” in his late thirties, with particular hand, foot, and hat size enlargement of the prior 3 years. He reported fatigue, arthralgias, oily skin, and decreased libido. He denied a family history of endocrine disorders. Physical examination was notable for a blood pressure of 151/83 mm Hg, rate-controlled atrial fibrillation, weight = 147 kg, height = 6’7”, and body mass index = 37. The patient appeared to be acromegalic, with frontal bossing, coarse facial features, enlarged nose, macrognathia, macroglossia, and widened interdental spaces. His hands and feet were enlarged and he exhibited pedal edema.

Laboratory tests confirmed acromegaly, with a serum insulinlike growth factor 1 (IGF-1) level of 560 ng/mL (81–225 ng/mL) and GH level of 16.7 ng/mL (0.05–3.00 ng/mL). Pituitary MRI showed an enlarged ES with subtle left anterolateral pituitary tissue but no distinct intrasellar adenoma; however, a sphenoid sinus mass extending from the infundibulum was also visualized, projecting inferiorly from the sellar floor (►Fig. 1). This seemed suggestive of a bone-enclosed ectopic pituitary tumor; however, further confirmatory work-up was felt indicated as such a tumor had not previously been described.

Pan-computed tomography (CT) with contrast demonstrated gross cardiomegaly but was otherwise negative for concerning masses.^{1,11} In-labeled octreotide scintigraphy was also unremarkable, and further work-up to rule out

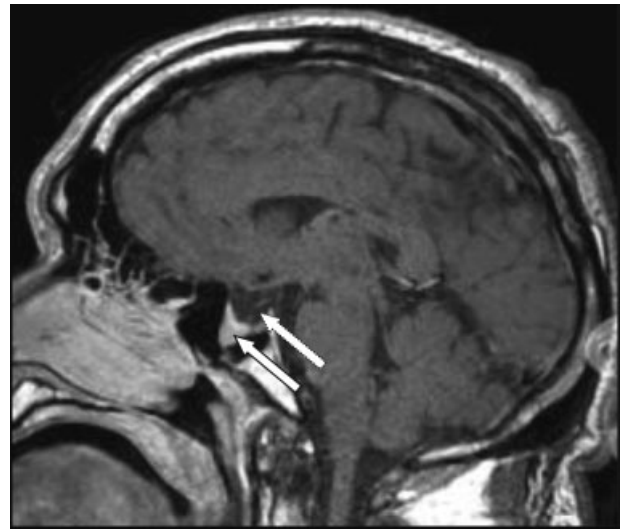


Fig. 1 Initial magnetic resonance imaging scan of the head. Sagittal enhanced spin echo T1 thin section through the sella shows a mass in the sphenoid sinus (solid arrow) in continuity with the infundibulum, and an empty sella (dotted arrow) with tissue along its floor.

possible GH hypersecretion was not immediately pursued as per the patient’s request. The patient was treated briefly with octreotide, but self-discontinued this due to visual hallucinations and declined further medical or surgical therapy.

The patient was lost to follow-up for over a year. Repeat laboratory tests showed persistent acromegaly (GH: 6.37 ng/mL; IGF-1: 771 ng/mL), and a 75-g oral glucose tolerance test failed to suppress GH. Other pituitary-axis hormones including prolactin (10.4 ng/mL; reference: 2.1–17.7 ng/mL) remained normal. Brain CT again did not recognize distinct tumor, but demonstrated stable ES configuration and unknown subsellar tissue within the bony intersphenoid septum (►Fig. 2). A low-normal GHRH level of 7 pg/mL (5–18 pg/mL) ruled out an ectopic neuroendocrine tumor, and repeated.^{1,11} In-labeled octreotide scintigraphy was negative. The patient continued to decline surgery and therefore was resumed on octreotide, but he again discontinued this due to side effects.

He was hospitalized several months later for obstructive gastrointestinal symptoms. IGF-1 level was unexpectedly normal at 92 ng/mL (confirmed on recheck 1 week later with IGF-1 level of 174 ng/mL); IGF-binding protein-3 was elevated at 6,430 ng/mL (2,592–4,770 ng/mL), ruling out elevated free IGF-1. Pituitary MRI again revealed an ES without evidence of hemorrhage or infarction, and stable tissue-filled bony projection from the sellar floor extending into the medial aspect of the sphenoid sinus (►Fig. 3). Given the patient’s normalized IGF-1 and absence of distinct intrasellar pituitary adenoma on imaging, spontaneous remission of acromegaly was considered; however, 75-g oral glucose tolerance testing failed to suppress GH. Petrosal sinus sampling showed an approximately six- to sevenfold central-to-peripheral GH gradient (peripheral = 3.27; left = 17.80; right = 20.20), consistent with central GH production.



Fig. 2 Coronal and sagittal computed tomography (CT) head. Left: Coronal enhanced CT scanning through the midsella using a bone window demonstrates the widened intersphenoid septum containing ectopic pituitary tissue (solid arrow). Right: Sagittal enhanced CT shows a sellar floor defect, enhancing pituitary tissue within the intersphenoid septum (dotted arrow) and marginally lining the sellar floor.

A direct endoscopic endonasal transsphenoidal approach was used to explore the sella turcica. A midline sphenoid sinus septa was resected, and the anterior wall and floor of the sella turcica were removed. The dura overlying the pituitary gland extended into an expansion of the sphenoid sinus; this dura was resected, revealing underlying soft tumor tissue that was removed using ring curettage and suctioning. Posterior to this tissue, normal pituitary gland tissue was identified.

Histology confirmed a typical pituitary adenoma, with cells that were positive for both human GH and prolactin by immunohistochemistry (► **Fig. 4**). Twenty-four hours after surgery, GH level was normal at 1.65 ng/mL (0.05–3.00 ng/mL), and other pituitary hormones remained within normal limits. Follow-up IGF-1 level 2 months after surgery was 67 ng/mL.

Discussion

Acromegaly stems from GH-secreting pituitary tumors in approximately 99% of all cases, and most tumors are visible on MRI of the sella.¹⁰ Only six prior instances of acromegaly occurring with both radiographic ESS and an ectopic sphenoid sinus pituitary adenoma have been documented.^{14–19} While our patient's pituitary location *within the walls of the bony intersphenoid septum* was suggested by CT and MRI studies, it appears to be a unique anatomical variation not previously described. It was recognized as pituitary tissue only retrospectively, on collaborative interdepartmental review of intraoperative findings and imaging, highlighting the difficulty of intrabony adenoma identification. Since pituitary remnants

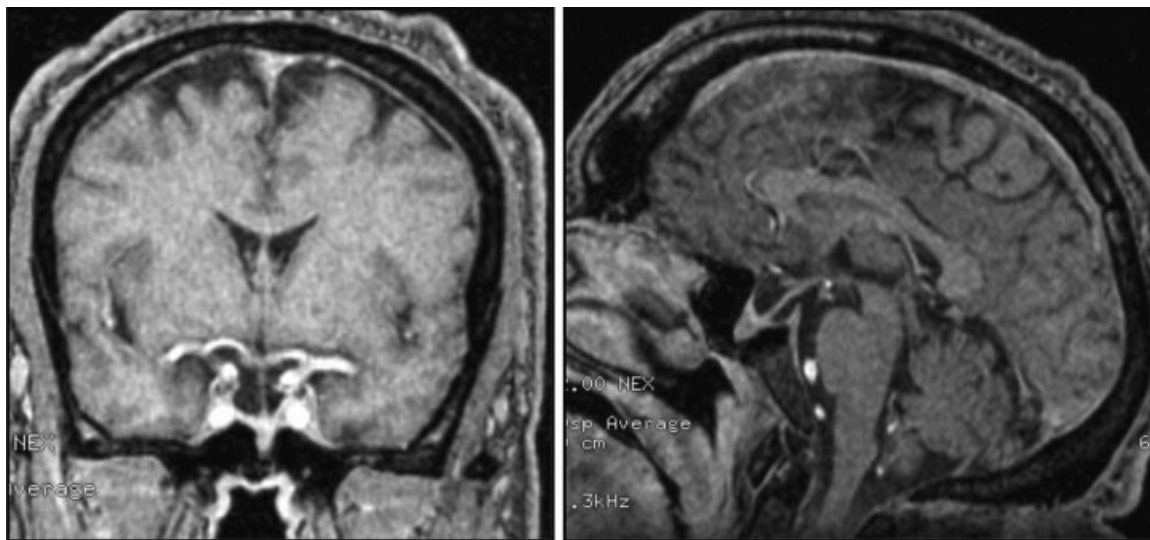


Fig. 3 Coronal (left) and sagittal (right) magnetic resonance imaging head scans. Enhanced fat-suppressed spin echo T1 images through the midsella demonstrate a stable mass in continuity with the infundibulum, extending below the sellar floor and into the widened intersphenoid septum.

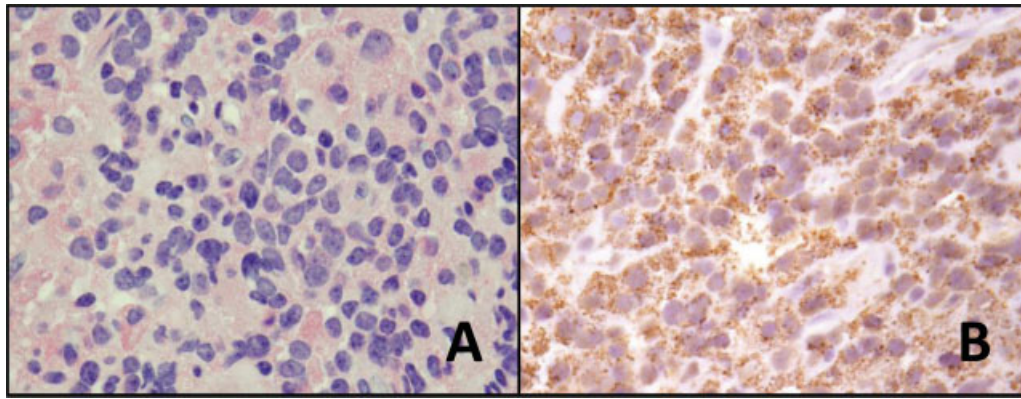


Fig. 4 Pituitary adenoma with growth hormone (GH) secretion. Formalin-fixed, paraffin-embedded tissue histology demonstrates pituitary adenoma (A: 1,000 \times magnification; hematoxylin–eosin stain) and GH secretion (B: 1,000 \times magnification; polyclonal rabbit antihuman GH antibody). Tissue also stained positive for prolactin (not shown).

laying outside the hypophyseal portal system may be less susceptible to normal hypothalamic regulation,²⁰ it is possible that other cases of intrabony adenomas within the intersphenoid septum have gone unrecognized in patients with pituitary hormone dysregulation and ESS/unidentified tumor.

It is unclear how this patient's pituitary anomaly developed. Ectopic pituitary tissue is most often situated in the sphenoid sinus or nasopharynx¹⁴ and is felt to result from faulty embryological migration and invagination course of Rathke's pouch, or mechanical adenoma protrusion through sellar floor defects (especially in conjunction with higher fluid-filled ES/intracranial pressure).^{19,21} Absent, eroded, and intact sellar floors were all described in six previously documented cases of acromegaly with combined ESS and sphenoid sinus ectopic adenoma¹⁴; our patient demonstrated an absent sellar floor. His enlarged sella and absent sellar floor might support a mechanical event—perhaps an originally larger macroadenoma which then hemorrhaged, necrosed, and involuted. Intracranial hypertension might then have led to an expanded sella along with caudal descent/flattening of the pituitary and extension into the intersphenoid septum, where the remaining tumor ultimately settled. Secondary ESS (and often, associated acromegaly remission) has been a documented sequela to pituitary apoplexy^{22–27}; however, increased intracranial pressure or aggressive tumor growth would theoretically displace the pituitary lateral to the intersphenoid septum along the path of least resistance, rather than induce a “split” configuration in the existing septal bone. Furthermore, our patient's earliest baseline MRI suggested primary ESS with no evidence of hemorrhagic or apoplectic evolution over several years of follow-up imaging, and while his IGF-1 levels decreased 5 years into his course, repeat oral glucose tolerance testing confirmed persistent biochemical acromegaly. Therefore, we postulate that our patient's clinical course and split bony septum (with smooth walls surrounding the ectopic pituitary) best support an anomalous embryological migration etiology, with baseline sellar floor incompetence also enabling his ultimate pituitary ectopy.

Treatment of patients with acromegaly and nonvisualized and/or extrasellar–sellar tumors poses a challenge to definitive acromegaly management, which generally demands

source localization followed by surgical tumor resection. To our knowledge, octreotide scintigraphy has been utilized in only one prior case of ectopic pituitary acromegaly, and that scan successfully identified the sphenoid sinus adenoma.¹⁴ However, our patient's scan was unremarkable, failing to reveal his intersphenoid septum tissue as an acromegaly-causative tumor.

Ultimately, our patient was successfully treated with transsphenoidal resection. His ectopic pituitary was demonstrated on serial CTs/MRIs, but was confirmed only retrospectively as pituitary tissue, due to lack of previously reported bony-encased intrasphenoid septal tumors and unfamiliarity with this diagnosis. Therefore, in his case, repeated testing and imaging were necessary to rule out a nonpituitary etiology and to better predict a central pathology amenable to neurosurgical resection. In this patient, a low GHRH ruled out an ectopic GHRH-secreting neuroendocrine tumor; and repeat.^{1,11} In-labeled octreotide scintigraphy, pan-CT, and petrosal sinus sampling ruled out a noncentral location.

Although our patient's tumor location within a bony septum is unique, its location in the sphenoid sinus was consistent with other extrasellar reports—12 of the 14 previously reported cases of “ectopic adenoma acromegaly” involved tumors within the sphenoid sinus.¹⁴ Our article demonstrates that in cases of central acromegaly, where imaging shows ESS and fails to identify an adenoma in paranasal sinuses or other peripheral locations, it is prudent to review MRI scans for a possible intra-intersphenoid septal tumor.

Disclosure

The authors have no multiplicity of interest to disclose.

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