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Case Report

Ectopic Growth Hormone-Secreting Pituitary Neuroendocrine Tumor in the Sphenoid Region: A Case Report of an Unusual Location of Tumor That Causes Acromegaly

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Abstract

Background: Acromegaly is almost always caused by a sellar growth hormone (GH)-secreting pituitary tumor, while ectopic pituitary neuroendocrine tumors (PitNETs) are exceedingly rare.

Case Presentation: This report a 44-year-old man with acromegaly and new-onset diabetes, whose sellar magnetic resonance imaging was normal but revealed a sphenoidal mass. Endoscopic transsphenoidal resection confirmed a GH-secreting PitNET. Postoperatively, he achieved biochemical remission and complete resolution of diabetes.

Conclusions: This case emphasizes the importance of considering ectopic PitNETs when acromegaly presents with normal pituitary imaging.

Keywords: Acromegaly, Pituitary neoplasms, Neuroendocrine tumors, Transsphenoidal surgery, Excessive growth hormone, Ectopic pituitary tumor

Citation: Jangsiripornpakorn J. Ectopic growth hormone-secreting pituitary neuroendocrine tumor in the sphenoid region: a case report of an unusual location of tumor that causes acromegaly. *Res Med J*. 20XX;XX(X):e281158. doi:10.33165/rmj.2027.e281158

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Received: 25 March 2026
Revised: 10 September 2026
Accepted: 11 September 2026
Published Online: 24 September 2026

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Introduction

Acromegaly is a chronic endocrine disorder characterized by excessive secretion of growth hormone (GH) and subsequent elevation of insulin-like growth factor 1 (IGF-1). This rare condition affects approximately 2.8-13.7 per 100 000 individuals in the population.[1] In over 95% of cases, acromegaly is caused by a benign GH-secreting pituitary adenoma located within the sella turcica.[2] Ectopic pituitary neuroendocrine tumors (PitNETs), which arise from embryological remnants of Rathke's pouch outside the sella, are an exceedingly rare cause of acromegaly, accounting for less than 1% of all acromegaly cases.[3, 4] The most common location for these ectopic tumors is the sphenoid sinus, followed by the suprasellar region, nasopharynx, and cavernous sinuses.[5-7] The diagnosis can be challenging, as the clinical presentation is identical to that of sellar disease, but sellar magnetic resonance imaging (MRI) is often normal. Herein, this present a case of a 44-year-old male with acromegaly caused by intrasphenoidal ectopic PitNET, highlighting the diagnostic journey and the successful clinical outcome following surgical intervention.

Case Presentation

A 44-year-old man was referred to the endocrinology clinic for the evaluation of progressive physical changes highly suggestive of acromegaly. For several months, he had

developed coarse facial features, frontal bossing, and striking enlargement of the hands and feet. He also reported a history of hyperhidrosis (excessive sweating). These manifestations prompted investigation following a recent diagnosis of new-onset diabetes mellitus. Two months prior, he presented with polyuria and unintentional weight loss. Initial laboratory findings confirmed severe hyperglycemia, fasting plasma glucose was 297 mg/dL, and hemoglobin A_{1c} (HbA_{1c}) was 11.2%.

The patient's past medical history was notable for a large anterior neck mass evaluated 2 years earlier. Physical examination at that time revealed bilateral thyroid nodules (right lobe 8 × 6 cm, left lobe 5 × 6 cm). Thyroid function tests showed suppressed thyroid stimulating hormone (TSH) (0.05 μIU/mL) with free thyroxine (FT4) and free triiodothyronine (FT3) in the normal range. He subsequently underwent a total thyroidectomy, and histopathology confirmed nodular hyperplasia without evidence of malignancy. Postthyroidectomy, he was appropriately commenced on levothyroxine replacement, maintaining a euthyroid state

Biochemical evaluation confirmed the diagnosis of acromegaly. Serum IGF-1 was markedly elevated at 882.0 ng/mL (reference range, 92.4-221 ng/mL), and baseline serum GH was 26.2 ng/mL (reference range, 0.03-2.47 ng/mL). A 75-g oral glucose tolerance test (OGTT) demonstrated persistent GH hypersecretion, with a nadir value of 25 ng/mL, confirming the lack of physiological suppression. Evaluation of other pituitary axis showed a morning cortisol level of 5.56 μg/dL and a reduced total testosterone of 222.55 ng/dL. MRI of the sellar region revealed a normal-appearing pituitary gland. However, a distinct, enhancing soft-tissue mass was visualized within the sphenoid sinus, raising the suspicion of an ectopic PitNET (Figure 1).

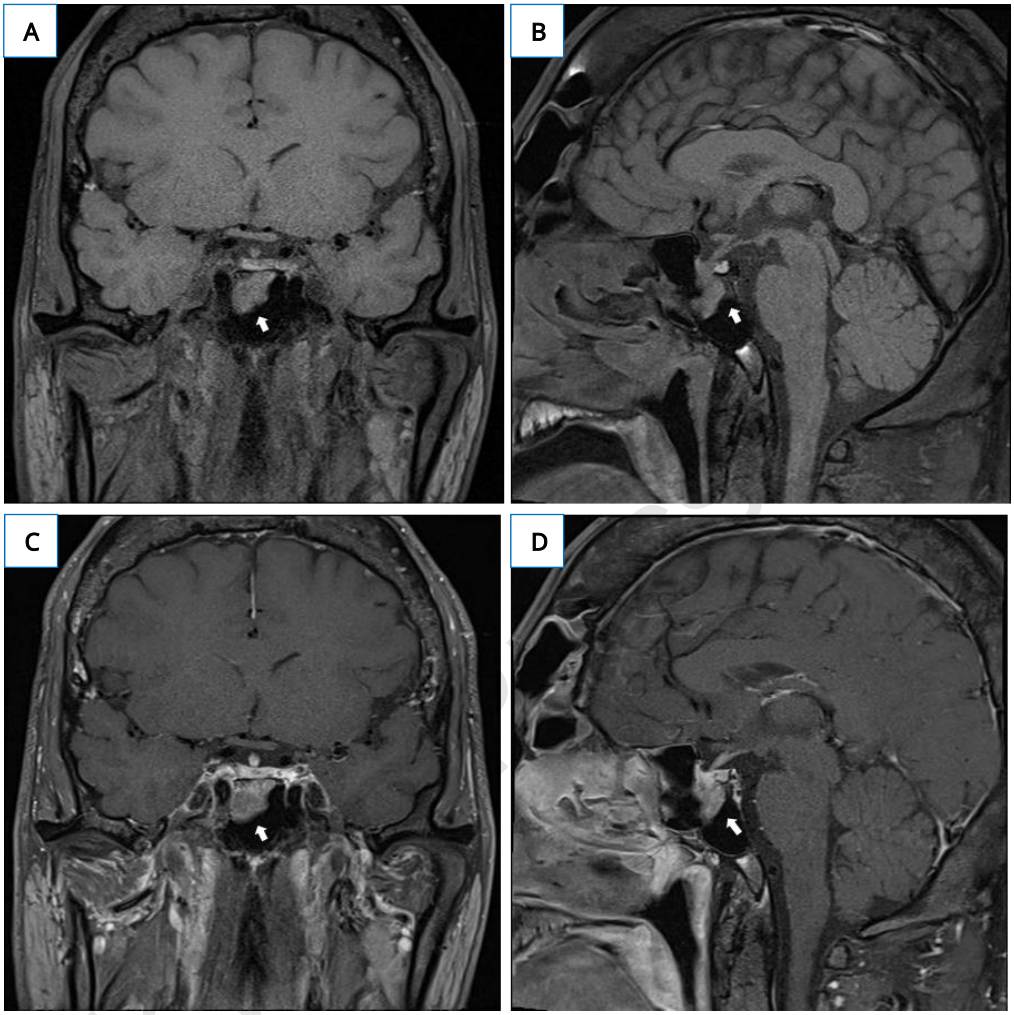
Based on the findings, a diagnosis of acromegaly secondary to an ectopic sphenoidal PitNET was made. The patient underwent an endoscopic transsphenoidal surgical resection of the tumor utilizing a surgical navigation system. Intraoperatively, the sellar floor was confirmed to be completely intact. The pituitary gland within the sella was left undisturbed, confirming the purely ectopic nature of the tumor, which was then completely removed from the sphenoid sinus.

Histopathological examination of the resected tissue showed a neoplasm composed of uniform cells with round nuclei and eosinophilic cytoplasm, consistent with a PitNET. Immunohistochemical staining was diffusely positive for synaptophysin and positive for GH. Staining was focally positive for prolactin but negative for TSH, adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The Ki-67 proliferation index was low (< 3%). The final diagnosis was a GH-secreting PitNET (Figure 2).

The patient's postoperative recovery was excellent. Follow-up laboratory tests performed at 3 months postoperatively confirmed biochemical remission, with a random GH of 0.83 ng/mL and a normalized IGF-1 of 220 ng/mL. Postoperative evaluation demonstrated intact function of other pituitary axes, evidenced by a normal morning serum cortisol level of 13.24 μg/dL, adequate thyroid hormone replacement status (FT4, 1.68 ng/dL [reference range, 0.92-1.68 ng/dL]; TSH, 3.11 μIU/mL [reference range, 0.27-4.20 μIU/mL]), and normal sex hormone levels. The status of diabetes mellitus was in remission, with a postoperative fasting blood sugar of 103 mg/dL and an HbA_{1c} of 5.5% without the need for antidiabetic medication. A follow-up MRI performed 6 months after surgery demonstrated expected postsurgical changes, including a widened sella and complete disappearance of the previously identified sphenoidal mass. An enhancing glandular tissue was noted at the anterior aspect, representing the normal pituitary gland. These imaging findings were consistent with successful tumor resection (Figure 3).

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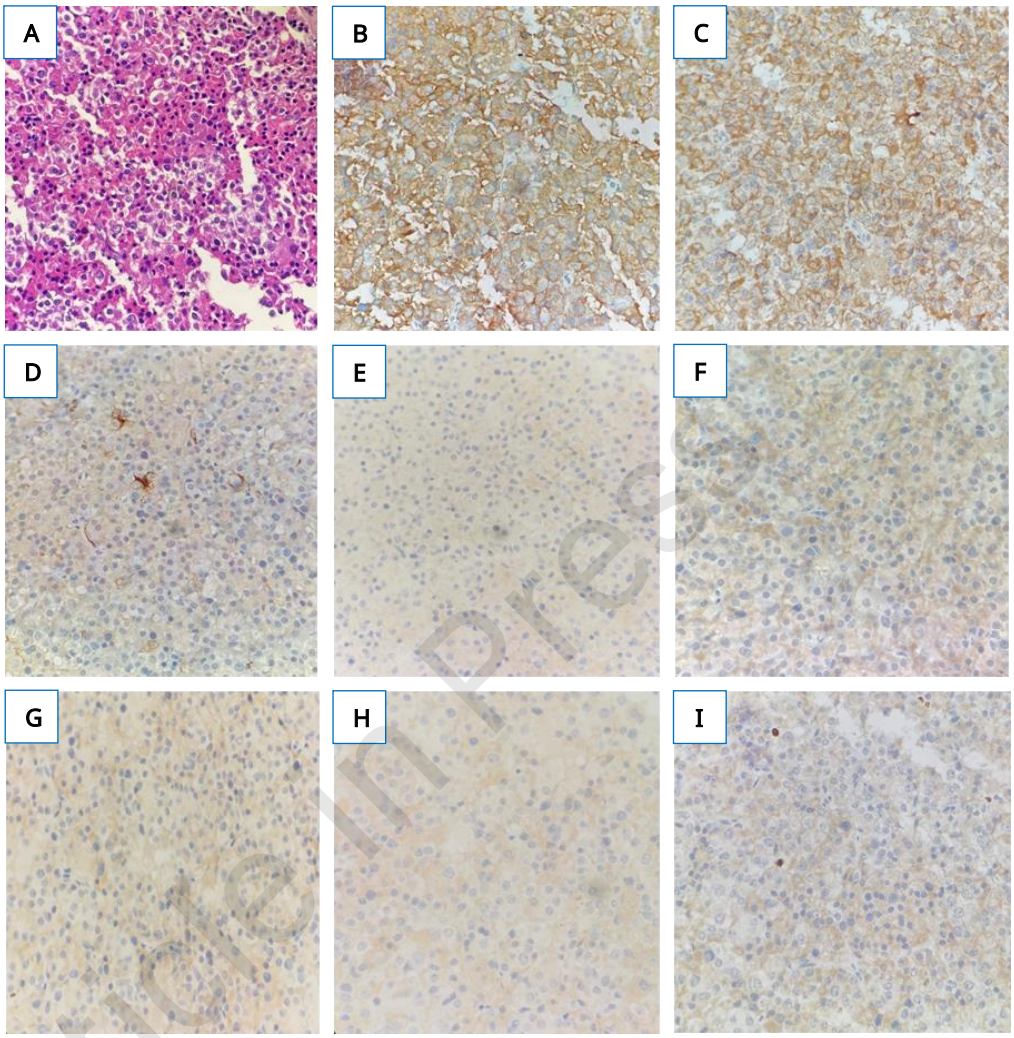
Figure 1. Preoperative Magnetic Resonance Imaging of the Sellar and Sphenoid Sinus



Coronal and sagittal views (T1-weighted [A and B] and postgadolinium T1-weighted [C and D]) demonstrated a normal intrasellar pituitary gland and a distinct soft-tissue mass (arrow) located solely within the sphenoid sinus, which showed enhancement on the postgadolinium images (C and D).

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Figure 2. Histopathological and Immunohistochemical Findings of the Ectopic Growth Hormone-Secreting Pituitary Neuroendocrine Tumor



A, Hematoxylin and eosin staining showed a neoplasm composed of relatively uniform cells with round nuclei and eosinophilic cytoplasm, consistent with a pituitary neuroendocrine tumor (PitNET).

B, Immunohistochemical staining showed diffuse positivity for synaptophysin.

C, Immunoreactivity for growth hormone (GH) showed diffuse positive.

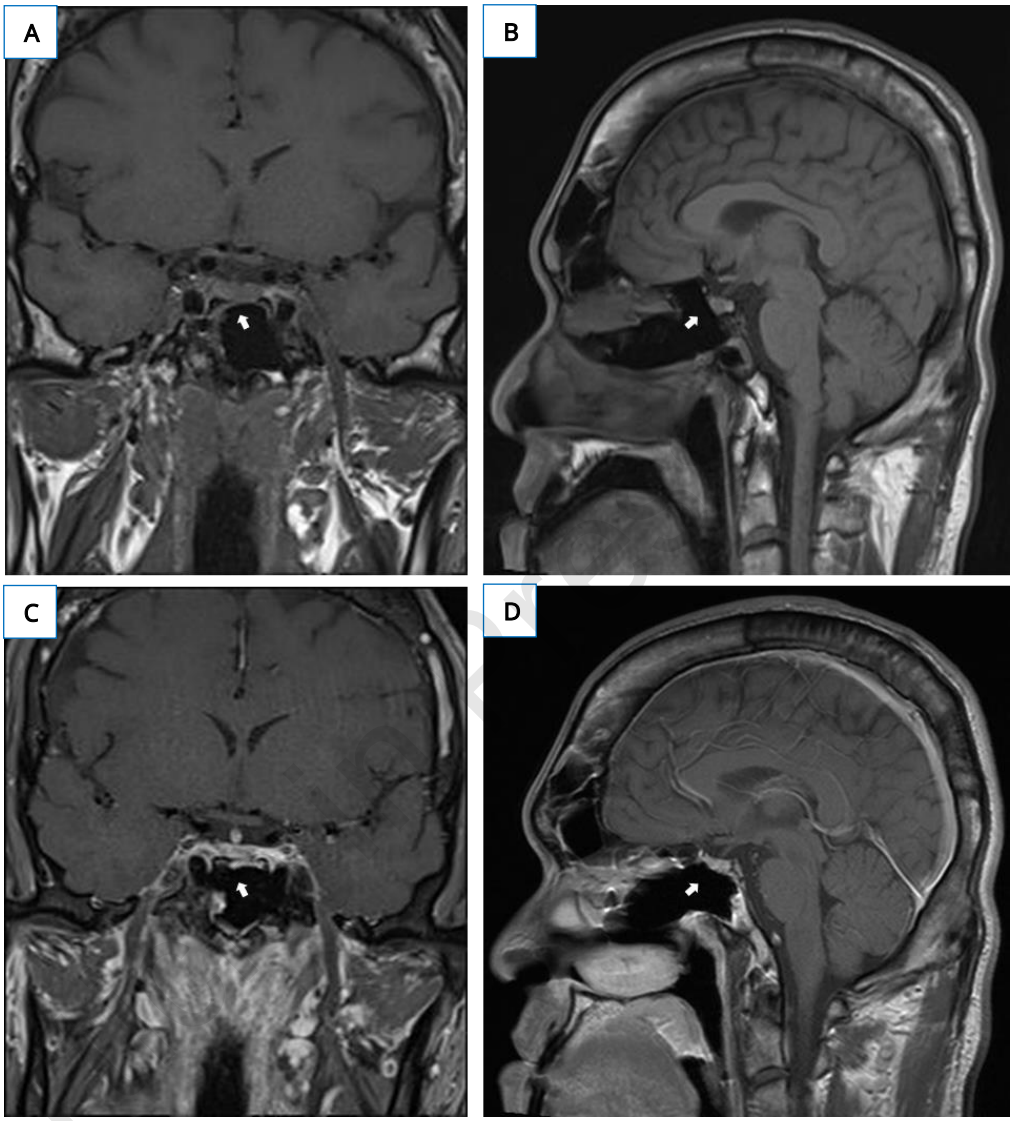
D, Immunoreactivity for prolactin (PRL) showed focal positive.

E-H, Immunoreactivity for thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), showed negative, respectively.

I, Ki-67 immunostaining showed a low proliferation index (< 3%). These findings were consistent with a GH-secreting PitNET.

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Figure 3. Six-Month Postoperative Magnetic Resonance Imaging of the Sellar and Sphenoid Sinus



Coronal and sagittal views showed expected postsurgical changes, including a widened sella and complete disappearance of the previously identified sphenoidal mass (T1-weighted images [A and B] and T1-weighted postgadolinium images [C and D]). Normal pituitary gland tissue (arrow) is noted at the anterior aspect.

Discussion

Based on the comprehensive literature review, this case of acromegaly caused by an ectopic GH-secreting PitNETs in the sphenoid region represents an exceptionally rare clinical entity. The updated 2022 WHO classification has introduced the term "pituitary neuroendocrine tumors (PitNETs)" to replace "pituitary adenoma", reflecting a more comprehensive understanding of these tumors' biological behavior and potential for invasiveness. Ectopic PitNETs are uncommon, accounting for less than 0.5% of all pituitary tumors.[2, 6]

The sphenoid sinus, as seen in this case, represents the most common location for these ectopic tumors, an anatomical predilection demonstrated in multiple case series.[1, 7-20] A summary of previously reported cases of ectopic GH-secreting PitNETs located in the sphenoid region (Table 1). This is attributed to the embryological development of the pituitary gland from Rathke's pouch. During normal organogenesis, this pouch forms from the oral ectoderm and should separate completely by gestational weeks 6-8. However, a failure of complete regression or aberrant migration of these embryological remnants can result in ectopic pituitary tissue along the craniopharyngeal canal, which is capable of subsequent neoplastic transformation. This complex developmental pathway is regulated by transcription factors like LHX3, PROP1, and PIT1; disruption of these programs can result in ectopic tissue formation, with the sphenoid sinus being a common site of arrest.[4]

The diagnostic challenge presented by such tumors lies in their identical clinical presentation to sellar adenomas, despite normal sellar imaging. In this case, the patient presented with classical acromegalic features, including coarse facial features, frontal bossing, acral enlargement, and hyperhidrosis, alongside new-onset diabetes mellitus. The biochemical profile confirmed active acromegaly, with a markedly elevated IGF-1 and failure of GH suppression during an OGTT. The patient's diabetes is a well-established consequence of acromegaly, as excess GH induces insulin resistance through multiple mechanisms including increased hepatic glucose production, enhanced lipolysis, and direct antagonism of insulin action.[21] The complete resolution of diabetes following surgical cure strongly underscores this direct causal relationship.

Endoscopic transsphenoidal surgery, the gold standard for PitNETs, was successfully utilized to achieve complete resection of an ectopic tumor, leading to the normalization of both GH and IGF-1 levels.[2, 22] This outcome meets the 2023 consensus criteria for biochemical remission, supported by normal age-adjusted IGF-1 levels and a low nadir GH during a postoperative OGTT.[23] Histopathological examination confirmed the diagnosis of a well-differentiated, benign GH-secreting PitNETs, as indicated by a low Ki-67 proliferation index, which is consistent with the excellent clinical outcome.[6]

This case demonstrates that with proper selection, ectopic PitNETs can be cured, as evidenced by the excellent clinical outcome, complete biochemical remission, and resolution of diabetes mellitus. The success of the surgical intervention is confirmed by follow-up imaging showing complete tumor resection and normal residual pituitary tissue. Although long-term surveillance is important due to potential recurrence, complete resection offers an excellent prognosis. The resolution of diabetes mellitus postsurgery highlights the reversibility of GH-induced metabolic dysfunction and underscores the importance of early diagnosis and treatment of acromegaly to prevent irreversible complications.

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Table 1. Summary of Reported Cases of Ectopic Growth Hormone Secreting Pituitary Neuroendocrine Tumors in the Sphenoid Region

Source	Type of Study	No. of Patients	Preoperative Hormonal Study	Surgical Treatment	Postoperative Outcomes and Hormonal Study
Corenblum et al,[8] 1980	Case report	1	GH 46.8 ng/mL PRL 5 ng/mL	Transsphenoidal surgery; intrasellar pituitary explored/ biopsied	GH secretion did not normalize after initial ectopic tumor removal; subsequent imaging 1 year later showed an intrasellar mass, raising the possibility of associated intrasellar disease
Warner et al,[9] 1982	Case report	1	GH 33.3 ng/mL PRL 158 µg/mL	Transsphenoidal surgery; subsequent bromocriptine 7.5 mg/day	GH remained elevated 4 months postoperatively but normalized after bromocriptine; biochemical control maintained at 12 months
Madonna et al,[10] 2001	Case report	1	Serum GH reported as normal; tumor showed GH and TSH immunoreactivity	Transnasal endoscopic sphenoidotomy with biopsy/resection	Postoperative biochemical outcome incompletely reported in the available paper; histology confirmed GH-positive pituitary adenoma
Matsuno et al,[11] 2001	Case report	1	GH 97 ng/mL IGF-1 2.3 × ULN; PRL 140 ng/mL	Transsphenoidal surgery	Ectopic adenoma completely removed; postoperative biochemical improvement/remission reported
Hori et al,[12] 2002	Case report	1	GH 14.54 ng/mL PRL 26.3 ng/mL	Transsphenoidal surgery and sellar-floor reconstruction	GH decreased to 2.62 ng/mL and PRL to 18.6 ng/mL; postoperative MRI showed no residual tumor
Gondim et al,[13] 2004	Case report	1	GH 97 ng/mL IGF-1 2.7 × ULN PRL 17 ng/mL	Transsphenoidal resection	GH decreased to 1.1 ng/dL and IGF-1 to 439 ng/dL; MRI showed an empty sella with residual sphenoid sinus tissue, which was confirmed as scar tissue on repeat endoscopic exploration
Mitsuya et al,[14] 2004	Case report	1	GH 133 ng/mL IGF-1 731 ng/mL PRL 73.0 ng/mL	Transsphenoidal surgery (partial resection of cavernous sinus tumor)	Persistent elevation of GH (153.0 ng/mL) and IGF-1 (748.0 µg/mL), with decreased PRL (25.8 ng/mL); subsequently underwent Gamma Knife radiosurgery
Chan et al,[15] 2005	Case report	1	GH and IGF-1 extremely elevated	Transsphenoidal surgery followed by radiotherapy	Symptoms improved dramatically and GH/IGF-1 returned to normal (after adjuvant radiation and chemotherapy)
Bhatoe et al,[16] 2007	Case report and literature review	1	GH 30.6 ng/mL	Transsphenoidal surgery	OGTT at 3 months postoperatively showed suppression of GH to 0.5-1.6 ng/mL
Kurowska et al,[17] 2008	Case report	1	GH 4.3 ng/mL IGF-1 615 ng/mL (2.5 × ULN)	Preoperative somatostatin analogue, followed by transsphenoidal surgery	Complete resection; postoperative GH 0.18 µg/L and IGF-1 140 mg/L with normalization of GH suppression on OGTT

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Table 1. Summary of Reported Cases of Ectopic Growth Hormone Secreting Pituitary Neuroendocrine Tumors in the Sphenoid Region (Continued)

Source	Type of Study	No. of Patients	Preoperative Hormonal Study	Surgical Treatment	Postoperative Outcomes and Hormonal Study
Appel et al,[1] 2012	Case report and literature review	1	GH 6 ng/mL IGF-1 3.1 × ULN PRL 26 ng/mL	Transsphenoidal surgery	At 3 months, IGF-1 normalized to 227 ng/mL, and GH suppressed to 0.3 µg/dL after a 75-g glucose load, indicating biochemical remission
Hong et al,[18] 2012	Case report and literature review	1	GH 18 ng/mL IGF-1 1120 ng/mL (3.6 × ULN)	Transsphenoidal surgery	At 5 months follow-up, serum GH decreased to 2 ng/mL and IGF-1 to 290 ng/mL
Ramirez et al,[7] 2013	Case report and literature review	1	GH 7.7 ng/mL IGF-1 920 ng/mL (4.8 × ULN) PRL 12.27 ng/mL	Octreotide LAR preoperatively followed by endonasal transsphenoidal resection	Persistent biochemical activity after surgery (GH 5.8 ng/mL, IGF-1 3.26 × ULN); achieved biochemical control with combination therapy of octreotide LAR and cabergoline (GH 0.8 ng/mL, IGF-1 1.6 × ULN), with no residual tumor on MRI
Wan et al,[19] 2015	Case report and literature review	1	GH > 40 ng/mL	Transsphenoidal surgery	Postoperative serum GH normalized and tumor was completely removed
Cifuentes-Lobelo et al,[20] 2024	Case report	1	GH 5.6 ng/mL IGF-1 426 ng/mL	Endonasal transsphenoidal surgery; near-total resection (> 90%) after preoperative embolization of an incidental anterior communicating artery aneurysm	Postoperative improvement and normalization of IGF-1 (8.15 ng/mL) reported; no major complications
Current study	Case report	1	GH 26.2 ng/mL IGF-1 882 ng/mL (3.9 × ULN)	Transsphenoidal surgery	Tumor completely removed; GH within normal limits (0.83 ng/mL)

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting repeatable; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; PRL, prolactin; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

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Conclusions

This case demonstrates the successful diagnosis and management of acromegaly from a rare ectopic PitNETs. It highlights a critical clinical principle, when a patient has biochemically confirmed acromegaly but a normal pituitary MRI, an active search for an ectopic source, particularly in the sphenoid sinus, is mandatory. With appropriate clinical suspicion and expert surgical management, a complete cure with resolution of hormonal and metabolic complications is achievable, underscoring the potential for excellent outcomes in these rare cases.

Additional Information

Acknowledgments: The author would like to thank Chaiyot Siangprasertkij, neurosurgeon, for kindly reviewing the surgical video of the patient.

Ethics Approval: This report obtained ethical approval from the Bangkok Metropolitan Administration Human Research Ethics Committee (S029hc/68_NA) on 22 October 2025.

Financial Support: No financial support was provided for this study.

Conflict of Interest: The author declares no conflict of interest.

Declaration of AI Assistance: The author used generative AI tool, specifically Grammarly, in the preparation of this manuscript. The AI was utilized for language refinement, including grammar checking and improving overall clarity. All AI-generated content is based on real data and has been thoroughly reviewed and verified by the authors to ensure accuracy, validity, and integrity. The authors take full responsibility for the content presented.

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