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Cushing's Disease Caused by a Pit-1 Lineage Macroadenoma with ACTH and GH Co-Expression: Case Report and Literature Review

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Abstract. ***Background and Clinical Significance:*** Pituitary neuroendocrine tumors (PitNETs) co-expressing growth hormone (GH) and adrenocorticotropic hormone (ACTH) are exceedingly rare, with only 30 cases reported in the literature to date. The majority of these cases present with acromegaly or mixed clinical features. The presented case is exceptional as it describes a Pit-1-lineage pituitary macroadenoma with GH and ACTH co-expression, characterized by clinically dominant ACTH hypersecretion with silent GH expression.

Case Presentation: We report a case of a 31-year-old woman with progressive Cushing's syndrome features and biochemical evidence of ACTH-dependent hypercortisolism. Pituitary MRI revealed a 21×16.5×15 mm sellar–suprasellar macroadenoma. *Bilateral Inferior Petrosal Sinus Sampling* (BIPSS) was attempted but was unsuccessful due to unfavorable venous anatomy. Alternatively, a high dose dexamethasone suppression test confirmed the central pituitary origin of ACTH-dependent hypercortisolism. The patient underwent transsphenoidal adenomectomy, which was complicated by cavernous sinus bleeding. Unexpectedly, histopathological evaluation revealed a Pit-1-lineage somatotroph PitNET with focal ACTH and GH expression, as well as dopamine receptor D2 (DRD2) and somatostatin receptor 2 (SSTR2) positivity. Postoperatively, the patient developed diabetes insipidus, secondary adrenal insufficiency, and central hypothyroidism, as well as abducens nerve paresis due to cavernous sinus injury. Early biochemical remission was achieved, and repeat MRI imaging showed no residual tumor and demonstrated hemostatic material in the left cavernous sinus region consistent with the patient's left abducens nerve paresis.

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Conclusions: This case is an addition to the limited literature of 30 reported GH-ACTH PitNETs, underscoring the critical role of immunohistochemical (IHC) staining in refining diagnosis and prognosis. Identifying this rare lineage-discordant profile is essential, as it predicts a possible higher recurrence risk while simultaneously revealing pharmacologic treatment as a potential therapeutic option in case of recurrence.

Keywords: Pituitary neuroendocrine tumor (PitNET), Cushing's disease, Pit-1 lineage, GH-ACTH co-expression

Kušingo liga, kurią sukėlė Pit-1 linijos makroadenoma su ACTH ir GH raiška: atvejo aprašymas ir literatūros apžvalga

Santrauka. ***Įvadas ir klinikinė reikšmė****:* Hipofizės neuroendokrininiai navikai (PitNET), ekspresuojantys somatotropinį hormoną (STH) ir adrenokortikotropinį hormoną (AKTH), yra ypač reti – literatūroje iki šiol aprašyta tik 30 tokių atvejų. Dauguma jų pasireiškia akromegalija arba mišriais klinikiniais požymiais. Pristatomas atvejis yra išskirtinis, nes aprašoma Pit-1 linijos hipofizės makroadenoma su STH ir AKTH raiška, kuriai būdinga kliniškai vyraujanti AKTH hipersekrecija ir nebyli STH raiška.

Atvejo pristatymas*:* Aprašome 31 metų moters, kuriai pasireiškė progresuojantys Kušingo sindromo požymiai ir biochemiškai buvo patvirtintas nuo AKTH priklausomas hiperkortizolizmas, atvejį. Hipofizės MRT tyrimo metu aprašyta 21×16,5×15 mm dydžio seliarinė-supraseliarinė makroadenoma. Bandyta atlikti bilateralinį apatinių uolinių ančių mėginį (BIPSS), tačiau dėl nepalankios venų anatomijos procedūra buvo nesėkminga. Kaip alternatyva buvo atliktas didelių dozių deksametazono supresijos mėginys, juo patvirtinta centrinė nuo AKTH priklausomo hiperkortizolizmo kilmė. Pacientei atlikta transfenoidinė adenomektomija, kuri komplikavosi kraujavimu iš kaverninio ančio. Netikėtai histopatologinis tyrimas parodė Pit-1 linijos PitNET su židinine AKTH ir STH ekspresija bei teigiamu dopamino receptorių D2 (DRD2) ir somatostatino receptorių 2 (SSTR2) dažymusi. Pooperaciniu laikotarpiu pacientei išsivystė necukrinis diabetas, antrinis antinksčių nepakankamumas ir centrinė hipotirozė, taip pat *abducens* nervo parezė dėl kaverninio ančio pažeidimo. Pasiekta ankstyva biocheminė remisija, o pakartotinis MRT tyrimas nerodė likutinio naviko, tačiau kairiojo kaverninio ančio srityje buvo matoma hemostatinė medžiaga, kas siejama su pacientės kairiojo *abducens* nervo pareze.

Išvados: Šis atvejis papildo ribotą literatūrą apie 30 aprašytų STH-AKTH PitNET atvejų, kartu pabrėžiama kritinė imunohistocheminio (IHC) tyrimo svarba tikslinant diagnozę ir prognozę. Identifikuoti šį retą imunohistocheminį profilį yra būtina, nes šis tyrimas prognozuoja galimai didesnę recidyvo riziką, kartu atskleidžia farmakologinio gydymo kaip potencialios terapinės galimybės ligos recidyvo atveju svarbą.

Raktiniai žodžiai: Hipofizės neuroendokrininis navikas (PitNET); Kušingo liga; Pit-1 linija; STH-AKTH raiška.

Introduction and Clinical Significance

Cushing's Disease (CD) is a rare condition defined by inappropriate cortisol hypersecretion that is most commonly caused by *Adrenocorticotropic Hormone* (ACTH) secreting pituitary adenomas. The estimated annual incidence is 1.8–4.5 cases per million individuals, with a female-to-male ratio of approximately 4:1 [1]. Most cases are caused by pituitary microadenomas, whereas macroadenomas (more than 10 mm in diameter) comprise only 10–20% of Cushing's disease cases [2].

According to the 2022 WHO classification guidelines, *Pituitary Neuroendocrine Tumors* (PitNETs) associated with the Pit-1 transcription factor are most commonly linked to *Growth Hormone* (GH), prolactin (PRL), or *Thyroid Stimulating Hormone* (TSH) secretion, and they typically present clinically with acromegaly, hyperprolactinemia, or thyrotoxicosis [3]. Among all PitNETs, those expressing two or more pituitary hormones on immunohistochemical (IHC) staining account for an estimated 10–15% of cases, with most hormonal combinations following the dominant transcription factor lineage, most commonly, GH and PRL [4]. Among these cases, the concurrent expression

of GH and ACTH is exceptionally rare because these hormones originate from different transcription factor lineages, with only 30 cases besides ours having so far been reported in the literature to the best of our knowledge [4-9].

We present a rare case of CD caused by a Pit-1 lineage GH-ACTH macroadenoma in which the clinical picture was dominated by ACTH hypersecretion, which is rare even within this small subset of cases, and transsphenoidal surgery was complicated by cavernous sinus bleeding, with the postoperative course being complicated by hypopituitarism, transient diabetes insipidus and abducens nerve paresis.

Case Presentation

A 31-year-old healthy Caucasian woman, with no prior history of daily use of medications or family history of endocrine disease, was initially evaluated for sinusitis. An MRI of the head and paranasal sinuses incidentally revealed a cystic-solid pituitary mass measuring 19×16×14 mm, consistent with a sellar-suprasellar pituitary macroadenoma extending toward the optic chiasm without signs of compression and clear cavernous sinus invasion.

The patient was subsequently referred to an endocrinologist, where, during the visit, the patient reported amenorrhea lasting 2 months, constipation, a 30 kg weight gain over the past six years (including 6 kg during the preceding month), persistent headaches, and hypertension. The findings of the physical examination were a 'moon face', facial plethora, central fat accumulation in the breasts and abdomen, abdominal stretch marks, violaceous striae in the lumbar region, and a dorsocervical fat pad ('buffalo hump'). Her body mass index (BMI) was 32.9 kg/m², weight 80 kg, and blood pressure 150/100 mmHg. Initial laboratory testing revealed the following results: 9:00 cortisol 532.4 nmol/L, ACTH 63.8 ng/l (reference value <46 ng/l) (see **Table 1**). Based on the clinical presentation and laboratory findings, the patient was referred for hospitalization for further evaluation due to suspected Cushing's disease.

Table 1. Clinical laboratory findings at initial presentation and during postoperative follow-up

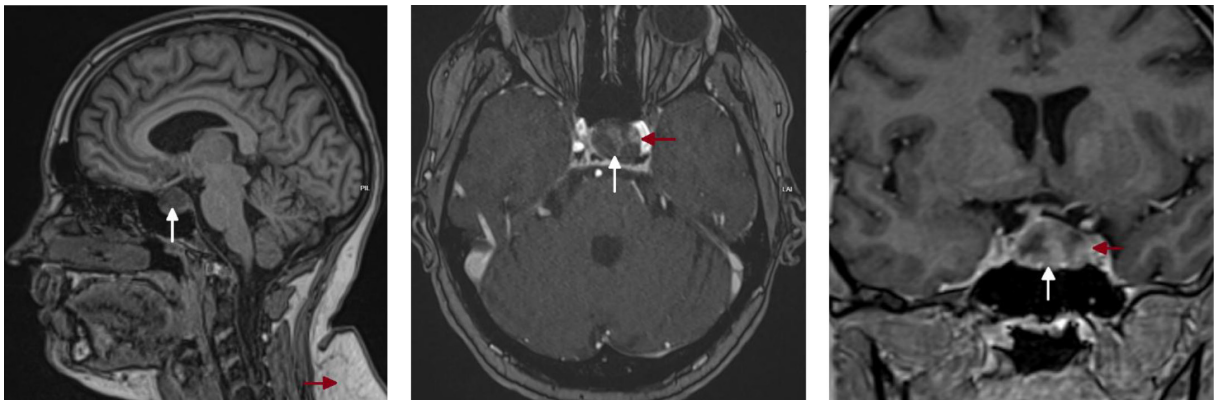
Test	Normal Range	Initial Results	Postoperative Day 7	Postoperative Day 30
Adrenocorticotropic hormone (ACTH)	<46.0 ng/L	**63.8**	**<5.0**	**<5.0**
Cortisol (COR)	101.0–536.0 nmol/L	532.4	**14.4**	**<13.8**
Free thyroxine (FT4)	9.0–19.0 pmol/L	12.1	10.4	9.55
Thyroid stimulating hormone (TSH)	0.4–4.0 mU/L	-	**0.08**	**0.215**
Prolactin (PRL)	108.7–557.1 mU/L	420.0	-	-
Insulin like growth factor 1 (IGF-1)	71.0-234.0 μg/L	185.0	-	-
Luteinizing hormone (LH)	-	0.7 U/L	-	-
Follicle-stimulating hormone (FSH)	-	1.4 U/L	-	-
Sodium (Na)	134.0–145.0 mmol/L	-	143	148
Potassium (K)	3.8–5.3 mmol/L	-	**5.9**	4.3
Urine specific gravity	1.000–1.030	-	1.021	1.020

Laboratory testing revealed a 23:00 cortisol level of 492.2 nmol/L (reference range at 23:00: 83.0–358.0 nmol/L). Additionally, a 1 mg overnight dexamethasone suppression test was also performed, which showed a 9:00 cortisol level of 149.4 nmol/L (reference range <50.0 nmol/L), indicating a lack of suppression. Confirmation of the diagnosis with *Bilateral Inferior Petrosal Sinus Sampling*

(BIPSS) could not be performed during the same hospitalization because of the recent exposure to dexamethasone during the suppression test and was therefore scheduled at a later date.

The patient was hospitalized again for BIPSS three weeks later in order to confirm the diagnosis, but the procedure was unsuccessful because venous anatomy could not be adequately visualized with contrast material, whereas catheter advancement was considered unsafe due to suspected narrow venous pathways. As an alternative, a *High Dose* (8 mg) *Dexamethasone Suppression Test* (HDDST) was performed: cortisol levels decreased from 531 nmol/L to 40 nmol/L, demonstrating a greater than 50% suppression and confirming the diagnosis.

A repeat MRI of the sellar region demonstrated a cystic-solid lesion that remained similar in size compared with the previous imaging findings but exhibited more prominent solid components **(Figure 1a, 1b, 1c)**. There was no evidence of cavernous sinus invasion or optic chiasm deformation. An urgent transsphenoidal neurosurgical intervention was indicated due to the severity of Cushing's disease based on the patient's clinical presentation, laboratory findings, and imaging results.



(**a**) (b) (c)

Figure 1. (**a**) T1-weighted sagittal MRI showing a 21x16.5x15 mm sellar lesion (previously measuring 19x16x14 mm) that is indicated with the white arrow. A dorsocervical fat pad is visible and is indicated by the red arrow. (**b**) Time-of-flight axial MRI demonstrating the same sellar lesion which is indicated by the white arrow. The lesion causes mild compression of the cavernous sinus on the left side marked with the red arrow and is in contact with approximately half of the diameter of the left internal carotid artery. (**c**) T1-weighted coronal contract enhanced MRI showing the same sellar lesion, indicated by the white arrow. Mild compression of the cavernous sinus on the left side is marked with the red arrow.

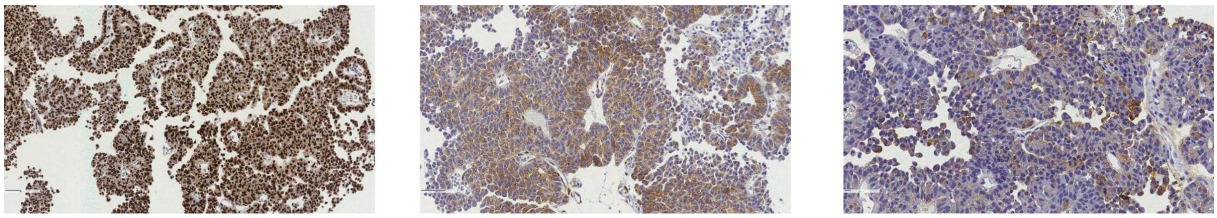
Transsphenoidal neurosurgical adenomectomy was performed, and the procedure was complicated by intraoperative bleeding due to injury of the cavernous sinus. Histopathological evaluation revealed a Pit-1–lineage somatotroph PitNET with focal ACTH and GH positivity on IHC staining, with positivity for both DRD2 and SSTR2 (see **Table 2, Figure 2**). Following the surgery, the patient was treated in the intensive care unit for three days, where the patient initially experienced nausea and headaches, which were managed medically and gradually resolved during hospitalization.

During the first 24 hours after surgery, intravenous hydrocortisone was administered continuously at a total dose of 100 mg. Shortly after the operation, episodes of marked polyuria of (>500 mL/h) were observed, resulting in a total diuresis of 6.8 L/24 h under adequate fluid replacement. Laboratory evaluation confirmed a low urine specific gravity of 1.007 and severe hypernatremia (up to 168 mmol/L). These findings established the diagnosis of diabetes insipidus, which was urgently managed with several intravenous doses of desmopressin (1–2 μg each) and intensive intravenous crystalloid infusions, resulting in a reduction of serum sodium to 156 mmol/l on the same day and 148 mmol/L on the second postoperative day. A lumbar drain was inserted to prevent *Cerebrospinal Fluid* (CSF) leakage.

On the second postoperative day, hydrocortisone therapy was transitioned from intravenous to oral administration of 40 mg/day (20 mg in the morning, 10 mg at noon, and 10 mg in the afternoon), and, due to recurrent episodes of polyuria and hypernatremia (148 mmol/L), sublingual desmopressin was initiated at a dose of 60 μg BID. Persistent left abducens nerve paresis was observed with no other focal neurological deficits. A brain CT performed two days after the surgery showed no acute intracranial bleeding. However, a repeat CT scan five days later demonstrated new haemorrhagic, dense material within the sphenoidal sinus and superior nasal passages, together with small air inclusions **(Figure 3)**.

Table 2. Histopathological IHC staining results

Marker	Staining result	Intensity & Pattern
Pit-1	Positive (+++, 100%)	Strong, nuclear
SF-1	Negative	
ACTH	Positive (++, 5%)	Moderate, cytoplasmic
GH	Positive (+++, 10%)	Strong, cytoplasmic
PRL	Negative	
TSH	Negative	
Dopamine Receptor D2 (DRD2)	Positive (+++, 100%)	Weak-Strong, membranous
Somatostatin Receptor 2 (SSTR2)	Positive (++, 10%)	Moderate, membranous
CAM5.2	Positive (++, 10%)	Strong, cytoplasmic/membranous
Ki-67 Index	Positive (+++, <3%)	Strong, nuclear



(**a**) (b) (c)

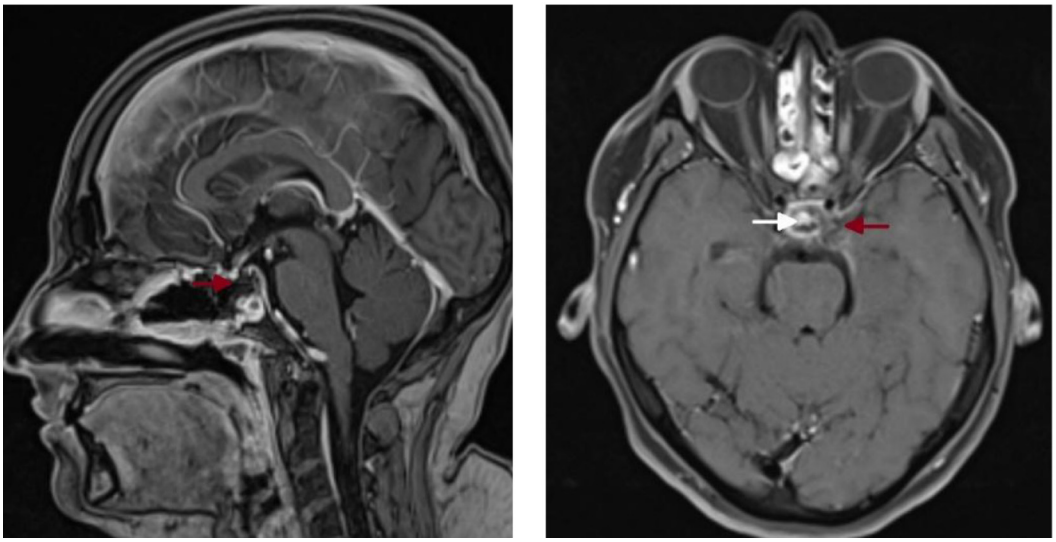
Figure 2. (**a**) IHC staining for Pit-1 (+3, ×20 magnification) (**b**); IHC staining for GH (+3, ×40 magnification); (**c**) IHC staining for ACTH (+2, ×40 magnification)



Figure 3. Non-contrast CT scan of the brain performed five days after transsphenoidal adenomectomy. Newly developed hemorrhagic, dense material, marked by the red arrows, is seen within the sphenoidal sinus and superior nasal passages, accompanied by small air inclusions

Further treatment and evaluation were carried out over the following two weeks in both the Neurosurgery and Endocrinology departments. Laboratory testing performed on the seventh postoperative day showed findings of hyperkalemia (K^+ 5.9 mmol/L), normal sodium concentration (Na^+ 143 mmol/L), central hypothyroidism evidenced by inappropriately suppressed TSH (0.08 mIU/L) in the presence of borderline low free T4 (10.4 pmol/L), and 9:00 cortisol of 14.4 nmol/L and ACTH <5.00 ng/L, which confirmed early biochemical remission after the surgical procedure (see **Table 1**). Urine specific gravity fluctuated within the normal range (1.010-1.021) while on sublingual desmopressin therapy of 60 μg BID, but it was later increased to 120 μg BID due to episodes of recurrent polyuria and hypernatremia (147 mmol/l). Levothyroxine was initiated at 50 μg once daily to address central hypothyroidism.

A follow-up MRI of the brain and pituitary gland was performed due to persistent left abducens nerve paresis – as imaging findings were consistent with postoperative changes following transsphenoidal adenomectomy and left cavernous sinus reconstruction, with the observed hemostatic material being the most likely cause **(Figure 4a, 4b)**.



(**a**) (b))

Figure 4. (**a**) T1-weighted sagittal contrast-enhanced MRI of the sellar region showing postoperative changes with no definite residual tumor. The red arrow indicates the remaining pituitary tissue, which appears to enhance with contrast material. (**b**) T1-weighted axial contrast-enhanced MRI with fat suppression showing postoperative changes after left cavernous sinus reconstruction and contrast-enhancing residual pituitary tissue denoted with the white arrow. Additionally, non-enhancing foci indicated with the red arrow extend from the left sella toward the dorsal cavernous sinus and Dorello's canal, likely representing hemostatic material

Hydrocortisone therapy was gradually tapered to a total daily dose of 30 mg (20 mg in the morning and 10 mg with the evening meal). The patient's condition subsequently stabilized, and she was discharged in good general condition with instructions for endocrinology follow-up after one month, although the left abducens nerve paresis remained, manifesting clinically as diplopia.

The patient presented to the clinic for outpatient follow-up approximately one month after the surgery. On physical examination, abducens nerve paresis was still observed. Laboratory testing was performed without taking the morning doses of hydrocortisone and levothyroxine and revealed partial recovery of the hypophyseal-thyroid axis, with Cushing's disease still in remission with the hypothalamic-pituitary-adrenal axis remaining suppressed (**Table 1**). From this point forward, the hydrocortisone dosage was tapered to a total daily dose of 25 mg (15 mg in the morning and 10 mg

with evening food), and the levothyroxine dose was increased to 100 μg. Regarding the gonadal axis, the patient reported persisting amenhorrhea, suggesting continued central hypogonadism for which biochemical markers (LH, FSH, estradiol) were not assessed at this early postoperative stage. The next outpatient follow-up appointment at the time of writing this report is at three months after the surgical procedure.

Discussion

Non-functioning pituitary adenomas are common incidental findings in up to 20% of the general population, whereas ectopic sources account for approximately 20% of ACTH-dependent Cushing's syndrome cases [1]. Therefore, bilateral inferior petrosal sinus sampling (BIPSS) remains the gold standard for distinguishing Cushing's disease from an ectopic ACTH source [10]. However, based on recently published consensus guidelines, with confirmed ACTH-dependent hypercortisolism and a pituitary macroadenoma on MRI, the diagnosis of Cushing's disease can be established with dynamic testing, without performing BIPPS [10].

In our case, BIPSS was pursued because the patient was initially reluctant to undergo surgery for the macroadenoma, and diagnostic confirmation was deemed essential before proceeding with operative management as the only available dynamic laboratory test to differentiate from ectopic ACTH-secreting sources was the high dose dexamethasone suppression test (HDDST), which has several shortcomings in terms of its sensitivity and specificity [10]. The estimated rate of successful bilateral inferior petrosal sinus cannulation is approximately 90%, with most unsuccessful procedures being attributed to anatomical variations, such as the absence of communication between the inferior petrosal sinus and the internal jugular vein or hypoplasia of the inferior petrosal sinus [11,12]. False-negative results occur in up to 10% of cases; consequently, it is recommended to use prolactin as a marker of correct catheter positioning, which helps to confirm normal inferior petrosal sinus venous efflux [11,12,13]. When BIPSS is unsuccessful, as in this case, dynamic tests such as the HDDST, the corticotropin-releasing hormone (CRH) test or the desmopressin test may be used as alternatives, although their sensitivity and specificity are lower than those of BIPSS [10]. The limitations of HDDST are well-documented in the literature, with studies demonstrating that an estimated 5–25% of ectopic ACTH tumors can demonstrate suppression, and, on top of that, up to 20% of patients with CD can fail to demonstrate suppression, which carries a substantial risk of misdiagnosis and unnecessary treatments [10,14,15]. Nevertheless, in this case, the HDDST revealed a cortisol decrease of more than 50%, which, in combination with the clinical, laboratory, and imaging findings of a macroadenoma, provided cumulative weight of evidence that was sufficient to establish the diagnosis.

The first-line treatment for Cushing's disease remains transsphenoidal endoscopic surgery, except in cases where the patient refuses surgical intervention or when surgery is not feasible due to the tumor location [10]. The rate of complications is low, and it primarily depends on the surgeon's experience and tumor characteristics such as the size and invasion of surrounding structures [16–20]. In our case, the postoperative course was complicated by well-recognized complications in the literature – notably, transient diabetes insipidus and anterior pituitary hormone deficiency, both of which were managed according to standard clinical protocols. Additionally, the patient developed a left abducens nerve paresis, a significantly rarer complication that could be attributed to bleeding that caused local swelling and transient compression of the intracavernous nerve fibers. It typically resolves within 3 months, with permanent cranial nerve deficits being extremely rare (<0.2%) and generally associated with direct nerve injury [21].

The peak serum sodium of 168 mmol/L observed in the immediate postoperative period underscores the volatility of water balance following pituitary surgery. This resulted from central diabetes insipidus (DI) that occurs in 10–30% of patients after pituitary surgery due to mechanical irritation

of the pituitary stalk or posterior lobe, which leads to disrupted ADH secretion [22]. It is also important to consider other possible causes such as osmotic diuresis secondary to glucocorticoid-induced hyperglycemia, excessive perioperative fluid administration, or natriuresis associated with a sudden drop in serum GH levels in patients presenting with acromegaly prior to surgery [22].

In our case, the diagnosis of central DI was confirmed by the triad of significant polyuria, low urine specific gravity, which excluded osmotic diuresis, and hypernatremia [23]. Retrospectively, the severity of the hypernatremia was likely exacerbated by a brief delay in the administration of intravenous desmopressin, after which, the polyuria and serum sodium concentration resolved. This highlights that, in the acute phase, meticulous monitoring is mandatory, and current best-practice guidelines recommend hourly measurement of the urine output and fluid intake, daily urine specific gravity, and serum sodium checks every 6–12 hours to allow for rapid therapeutic adjustments [22].

The classification of pituitary tumors, which express multiple hormones, has evolved significantly, with the 2017 WHO classification defining plurihormonal adenomas as tumors expressing more than two hormones on immunohistochemistry and the 2022 classification restricting this term to tumors in which multiple hormone expression is accompanied by the corresponding transcription factors [3]. Most of the literature predating the guidelines issued in 2022 describe GH-ACTH Pit-NET cases as plurihormonal adenomas without transcription factor staining, although some more recent reports also include transcription factor analysis and adhere to the more recent guidelines. Most frequently, PitNETs characterized by immunoreactivity for more than one pituitary hormone on IHC staining manifest with a clinical picture dominated by only a single hormone [4,24]. The combination that is the most common is that of GH and PRL; compared to it, the concurrent expression of GH and ACTH is an exceptional finding with only 30 cases besides ours being so far reported in the literature to the best of our knowledge [4–9] (**Table 3**). Among the 30 cases, 15 (50%) presented primarily with acromegaly, 7 (23%) with acromegaly and Cushing's disease, 3 (10%) with pituitary apoplexy, and isolated Cushing's disease was observed in only 5 cases (17%).

Table 3. Overview of clinical characteristics and immunohistochemical profile of ACTH-GH pituitary adenomas reported in the literature*

Author, Year	Age, Sex	Clinical Presentation	Elevated Laboratory Tests	Size	Histological profile (IHC)
Arita et al. (1991)	29, F	Acromegaly and CD	IGF-1, GH, cortisol	Macroadenoma	Diffuse GH and focal ACTH positivity
Blevins et al. (1992)	40, F	Acromegaly and CD	GH, UFC	Macroadenoma	Focal ACTH and GH positivity
Bugalho et al. (1993)	62, M	CD	ACTH	Microadenoma	Focal ACTH and GH positivity
Apel et al. (1994)	76, F	Acromegaly	ACTH, GH	Macroadenoma	Focal ACTH and GH positivity
Matsuno et al. (1996)	27, M	Acromegaly	ACTH, GH, PRL, cortisol	Macroadenoma	ACTH, GH, PRL, alpha subunit positive
Kovacs et al. (1998)	62, M	Acromegaly	GH, cortisol	Microadenoma	Diffuse GH with focal ACTH Positivity
Duskova et al. (2000)	75, F	Acromegaly	-	Macroadenoma	GH and ACTH cells, dispersed PRL, scattered cells positive for beta subunits of FSH, LH, TSH
Mazarakis et al. (2001)	53, M	Acromegaly	IGF-1	Macroadenoma	Diffuse ACTH with focal GH positivity

Author, Year	Age, Sex	Clinical Presentation	Elevated Laboratory Tests	Size	Histological profile (IHC)
Abe et al. (2001)	30, M	Pituitary apoplexy	ACTH, GH, cortisol	Macroadenoma	ACTH, with minority of GH positivity
	29, F	Pituitary apoplexy	ACTH	Microadenoma	ACTH, with minority of GH positivity
	59, F	Pituitary apoplexy	ACTH	Macroadenoma	Focal ACTH and GH positivity
Kageyama et al. (2002)	45, F	Acromegaly and CD	ACTH, IGF-1 cortisol	Macroadenoma	Focal ACTH and GH positivity
Tahara et al. (2002)	53, F	CD	ACTH, cortisol	Microadenoma	Same cells with positivity for ACTH and GH
Tsuchiya et al. (2006)	5, M	Acromegaly	ACTH, IGF-1, GH	Macroadenoma	Diffuse GH and PRL with focal ACTH positivity
Oki et al. (2009)	36, F	Acromegaly	GH, IGF-1	-	Diffuse GH and focal ACTH and TSH positivity
Zada et al. (2011)	31, F	Acromegaly	-	-	-
Kannan et al. (2012)	52, M	Acromegaly	ACTH, IGF-1, cortisol	Microadenoma	Sparse GH positivity, PRL positivity, small foci of ACTH positivity
Rajendran et al. (2013)	62, M	Acromegaly	GH, IGF-1, PRL	Macroadenoma	Diffuse ACTH with focal GH and PRL positivity
Rasul et al. (2014)	61, F	Acromegaly	GH, IGF-1, cortisol	-	Diffuse ACTH and GH positivity
	78, F	Acromegaly	GH, IGF-1, cortisol	-	Acidophilic cells with GH, focal PRL, a single area expressing ACTH and GH
Takiguchi et al. (2017)	45, F	Acromegaly and CD	ACTH, IGF-1, GH	Macroadenoma	Acidophilic cells with GH, focal PRL, sparse ACTH positivity
Roca et al. (2018) [5]	60, F	Acromegaly and CD	GH, IGF-1, ACTH, cortisol	Microadenoma	Cells positive for either GH or ACTH
Schwehr et al. (2021)	30, F	Acromegaly and CD	IGF-1, UFC, cortisol	Microadenoma	ACTH and Synaptophysin positive
Allehaibi et al. (2021)	65, F	CD and mass effect	ACTH, UFC, PRL	Macroadenoma	ACTH, GH, PRL positive
Fukunaga et al. (2021)	21, F	CD	ACTH, UFC, GH, IGF-1	Macroadenoma	Diffuse ACTH
Amir et al. (2022) [6]	35, F	Acromegaly and CD	Cortisol, UFC, IGF-1	Macroadenoma	Initially, T-Pit, Pit-1 and ACTH, GH, PRL positive. At recurrence, ACTH and GH positive
Gharroudi et al. (2023) [7]	35, F	Acromegaly	IGF-1, PRL	Macroadenoma	GH and ACTH positive
Kostyleva et al. (2024) [8]	65, M	Acromegaly	GH, IGF-1, cortisol, fT4, UFC	Macroadenoma	T-Pit, Pit-1 and ACTH, GH, TSH positive
Dumitriu-Stan et al. (2024) [4]	-, M	Acromegaly	ACTH, GH, IFG-1	Microadenoma	Strong GH and low ACTH positivity
El Idrissi Dafali et al. (2025) [9]	34, -	CD	ACTH, GH, Cortisol	Macroadenoma	GH and ACTH positive
Presented case	31, F	CD	ACTH, cortisol	Macroadenoma	Pit-1 with focal ACTH and GH positivity

**Note:* Data presented in this table have been adapted from the systematic reviews by Roca et al. [5] and Amir et al. [6], with additional updates and recent cases identified by the authors. Abbreviations in use: ACTH, adrenocorticotropic hormone; CD, Cushing's disease; fT4, free thyroxine; GH, growth hormone; IGF-1, insulin-like growth factor 1; PRL, prolactin; UFC, urine free cortisol.

The 2022 WHO classification emphasizes that transcription factors are essential in differentiating these tumors by helping to determine the cell lineage, it is recommended to stain for Pit-1 (GH, PRL, TSH), T-Pit (ACTH) and SF-1 (LH, FSH) [3]. Typically, Cushing's disease is driven by a T-PIT-lineage corticotroph PitNET, but in this case, IHC staining revealed a Pit-1-lineage somatotroph tumor demonstrating focal immunoreactivity for both GH and ACTH, with the clinical syndrome being exclusively ACTH-dependent (see **Table 2**) [3]. In the absence of T-PIT immunostaining, it is difficult to determine the exact mechanism underlying ACTH secretion in the presented case. The possible explanations include the presence of a minor corticotroph cell population within a predominantly somatotroph tumor or a lineage-discordant phenotype with multiple transcription factor positivity within the same cell population, both of which have been described in GH-ACTH expressing PitNET cases, with distinct cell populations within a single tumor reported as the more common mechanism [5]. Additionally, a rare differential diagnosis in such cases is the presence of synchronous multiple pituitary adenomas, which can present as two different GH and ACTH secreting lesions [25,26]. This phenotype is particularly distinct because the majority of reported GH-ACTH PitNETs present with acromegaly and elevated IGF-1 levels with subclinical or clinically silent ACTH secretion [4–9]. It has been hypothesized that this dominance of acromegaly is due to the secretion of high-molecular-weight ACTH, which is biologically inactive and does not trigger hypercortisolism despite positivity on IHC staining, or insufficient autonomous secretion of ACTH to cause hypercortisolemia with its associated symptoms [4].

The unique features of this case have significant implications for long-term prognosis. Firstly, the tumor's classification as a macroadenoma is a well-established predictor of lower surgical success based on a systematic review which included multiple meta-analyses that compared outcomes following transsphenoidal resection and demonstrated a significantly lower remission rate of 59.9% for macroadenomas compared to 85.5% for microadenomas, as well as a higher risk of recurrence estimated at 17% for macroadenomas compared to 9.8% for microadenomas [27]. Furthermore, PitNETs producing hormones from histogenetically unrelated lineages, especially those which are associated with ACTH co-expression, may display more aggressive biological behavior and higher recurrence rates [4,28]. However, this unusual IHC profile also offers a distinct therapeutic advantage. Typical T-PIT-lineage corticotroph tumors generally exhibit low DRD2 and SSTR2 expression and are frequently resistant to medical therapy, with only 20–25% of cases responsive to dopamine agonists and allowing long term control of hypercortisolism [29,30]. In contrast, our patient's tumor demonstrated strong positivity for DRD2, which suggests that, in the event of recurrence, targeted medical treatment with dopamine agonists could be a viable option as an alternative to repeat surgical treatment or radiotherapy. Supporting this hypothesis, there have been cases that described successful Cushing's disease management with cabergoline and pasreotide in similar cases of lineage-discordant adenomas [31,32,33].

Given the elevated recurrence risk associated with this specific IHC profile and the size of the excised tumor, a rigorous postoperative surveillance protocol is deemed essential. Early biochemical remission was confirmed in our patient by morning serum cortisol levels dropping below 50 nmol/L within the first week of surgery, which is a strong predictor of initial success [22]. The current plan of further reevaluation is at 3 months postoperatively, followed by assessment every 3–6 months until hypothalamic-pituitary-adrenal (HPA) axis recovery has been confirmed [10]. Nearly half of recurrences occur within the first five years; thus, long-term annual screening will be mandatory once the HPA axis recovers [1,10,22]. Furthermore, considering the tumor's confirmed Pit-1 lineage and silent GH expression, future surveillance will include IGF-1 measurement alongside standard cortisol testing. This is essential to detect any potential phenotypic shift or secondary hormone hypersecretion during recurrence, which was well illustrated by the case presented by Amir et al. [6].

Conclusions

This case contributes to the limited literature on rare GH and ACTH co-expressing PitNETs presenting as Cushing's disease. IHC staining is highly valuable in detecting these variants, which are difficult to suspect with solely biochemical results and clinical features given the variable presentation. The identification of a lineage-discordant IHC profile fundamentally alters the long-term management strategy and prognosis. While this profile may indicate a higher risk of recurrence, the strong expression of DRD2 identifies dopamine agonists as a potential therapeutic option in the case of recurrence. Strict long-term endocrine surveillance incorporating both cortisol and IGF-1 monitoring is mandatory to mitigate morbidity and a potentially higher mortality risk. Continued research and reporting of such cases are essential to better evaluate the recurrence risk, possible pathogenetic mechanisms, and treatment options.

Author contributions

J. J.: Conceptualization, Data Curation, Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing.
G. N.: Supervision, Validation, Writing – Review & Editing.
D. G.: Supervision, Writing – Review & Editing.
All authors have read and agreed to the published version of the manuscript.

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