Volume 1, Issue 2 (July-December 2025)
**Page No**: 100-104 | **e-ISSN: 3107-5738**

Case Report

# Delayed Detection of ACTH-Secreting Pituitary Microadenoma: A Case for Serial Imaging in Refractory Cushing's Disease

[1*]Zainab Haider Khan, [2]Dr. Natnael Fitsum Asfeha,[3]Dr.Lubna Mirza
[1]Avalon University School Of Medicine, Curacao, [2]Hallelujah General Hospital, Department of Internal Medicine, Ethiopia, [3]Norman Regional Healthcare, Department Of Endocrinology, USA

*Corresponding Email- zainabkhan3715@gmail.com
DOI: 10.64790/tsj.2025.v1.i2.27

*Received 23 November 2025 Revised 28 December 2025 Accepted 28 December 2025 Published 31 December 2025*

***ABSTRACT***
Cushing's disease (CD), a subtype of Cushing syndrome caused by pituitary ACTH-secreting adenomas, can be challenging to diagnose, especially in the presence of adrenal incidentalomas which can suggest adrenal cause shifting the focus away from the possibility of true pituitary disease in ACTH-dependent hypercortisolism.
**Case Presentation:** This case is presented as a 61-year-old female with an initial presentation of hypercortisolism who was diagnosed with adrenal Cushing syndrome after an MRI revealed a unilateral adrenal incidentaloma. She was gonadotrophically deprived and her adrenal gland was removed and she briefly improved. The symptoms reoccurred several years later and repeat imaging and inferior petrosal sinus sampling (IPSS) showed that she had an ACTH-secreting pituitary microadenoma. After transsphenoidal resection, the IGF-I of the patient was slightly elevated that created the suspicion of GH co-secretion even though there was no clinical sign of acromegaly. The patient has attained biochemical remission and she is under close follow up.
**Conclusion:** This case highlights the diagnostic complexity of CD in the presence of adrenal incidentalomas and emphasizes the importance of thorough hormonal workup, repeat imaging, and the use of IPSS. The deviation from the diagnostic guidelines for biochemistry and failure to recognize the initial normal levels of ACTH could have eliminated the delayed diagnosis.

**Keywords: Cushing's Disease, ACTH-secreting adenoma, GH co-secretion, pituitary tumor, adrenal incidentaloma, diagnostic delay**

## 1. INTRODUCTION

Cushing syndrome comprises signs and symptoms associated with prolonged exposure to abnormally high levels of plasma glucocorticoids. Untreated, it has significant morbidity and mortality(1). Cushing disease is defined as the specific type of Cushing syndrome due to excessive pituitary ACTH secretion from a pituitary tumor(2). Despite the progress in biochemical evaluation and imaging, diagnosing and managing CS in some patients continues to be a challenge(1). Established guidelines recommend that the diagnosis should be confirmed with at least two different biochemical tests, such as elevated 24-hour urinary free cortisol (UFC), lack of suppression on a low-dose dexamethasone test, or elevated late-night salivary cortisol.

Cushing's disease (CD) involves achieving a precise diagnosis, carefully selecting treatment, and managing patients over their lifetime to optimize outcomes(4). This case helps to illustrate the complex and often confusing diagnostic pathway for patients with Cushing's disease - particularly when 'adrenal incidentalomas' can suggest an adrenal cause for the condition at presentation. The presence of adrenal incidentalomas further might shift focus away from the possibility of true pituitary disease in ACTH-dependent

hypercortisolism. Following adrenalectomy, the patient had symptom recurrence along with biochemistry for ACTH-dependent hypercortisolism and was subsequently re-diagnosed, with her disease source ultimately being in the pituitary.

## 2. CASE PRESENTATION

A 61-year-old woman was referred to Endocrinology in August, 2019 due to elevated cortisol levels. Her other significant symptoms were weight gain despite her healthy lifestyle, being prone to bruising and bleeding with minor incidents, posterior neck fat deposition (buffalo hump) for which she underwent liposuction surgery in April, 2019. Lab work was drawn to identify the possible endocrine abnormalities(Table:1). Initial workup showed an elevated 24-hour urinary free cortisol (UFC). However, per guideline recommendations, a second confirmatory test (e.g., dexamethasone suppression test or late-night salivary cortisol) was not performed at this stage. Post her abnormal cortisol workup, brain MRI was scheduled to identify any possible adenoma.

The results of MRI were conclusive for no pituitary mass with convincing evidence of normal pituitary size. Notably, the initial serum ACTH level was 29 pg/mL, which is within the normal range but crucially non-suppressed. This finding is indicative of ACTH-dependent Cushing's syndrome rather than a primary adrenal etiology, in which ACTH is typically suppressed. Further imaging using CT scan of chest, abdomen, pelvis was performed to identify the ectopic source of ACTH along with this dexamethasone suppression test with detailed lab work was performed. CT scan showed the evident presence of left adrenal adenoma of size 1.6cm. The dexamethasone suppression test demonstrated the abnormally high cortisol with continued elevated 24 hr. urine cortisol along with this other lab test were within the reference range(Table:1). With the presence of clinical, imaging and laboratory evidence she was diagnosed with Cushing syndrome.

The treatment plan was surgical removal of the left adrenal gland in December,2019. Post left adrenalectomy the surgical pathology showed the presence of a second tumor 0.3 x 0.3 cm in size.

Post-op she was on a temporary steroid dose (20mg BID) which was tapered over 6+ weeks. Follow-ups showed significant improvement in her symptoms along with normalized serum cortisol at 18.7 µg/dL and ACTH at 36 pg/ml.

**Table.1:- Lab Reports**

| Parameter | Pre-Adrenalectomy | Post-Adrenalectomy | 2023 |
|---|---|---|---|
| Serum Cortisol (8 AM) | 27 µg/dL (4.0–22) | – | – |
| Serum ACTH (8 AM) | 29 pg/mL (9–52) | – | 48 pg/mL |
| 24-Hour Urine Cortisol | 130.5 µg/24 hr (Ref: 3.5–45) | 133.9 µg/24 hr | 46 µg/24 hr |
| 1 mg Dexamethasone Suppression Test | – | Cortisol 19.5 µg/dL | Cortisol 11 µg/dL |
| DHEA | – | 171 µg/dL (Ref: Females ≥60 yr: <145) | 140 µg/dL |
| Electrolytes | Within reference range | | |
| TSH, TPO | Within reference range | | |
| Aldosterone & Renin | Within reference range | | |
| Urine Metanephrines & Catecholamines | Within reference range | | |

However, after this course of her treatment the symptoms reappeared in 2022 and she decided to come back to the clinic in 2023.Her symptoms included fatigue, easy bruising, thin skin, mood changes, sleeping issues raised concerns that either she had a persistent or a new source of cortisol secretion. After a full endocrine evaluation her labs showed overall elevated cortisol levels(Table:1).

Further, evaluation with brain MRI was performed which showed no evidence of mass or any other morphology change and size of the pituitary with homogeneous contrast enhancement raising a concern of exogenous cortisol production. CT scan of chest, abdomen, pelvis was performed which was positive for new right 1.1cm adrenal adenoma. The treatment plan of right adrenal gland removal leading to chronic adrenal insufficiency was discussed. After this encounter the patient underwent a back surgery in June,2024.

Patient opted for a second opinion at MD Anderson Houston, where repeated brain MRI imaging was performed which showed a possible tumor. The test was either more sensitive or the tumor was grown but ultimately believed to be the cause of the new adrenal mass on the right side, pituitary- driven ACTH overproduction.

For definitive diagnosis an Inferior Petrosal Sinus Sampling (IPSS) procedure was performed which provided the diagnosis of left side ACTH secreting pituitary tumor giving Cushing disease as her final diagnosis.

This new diagnosis led to transsphenoidal surgical resection of the tumor in August 2024. Her post-surgical follow ups indicated elevated level of IGF-1 which was deemed to be insignificant but her cortisol levels, ACTH levels were within the reference range. Another brain MRI performed post-op showed no abnormality indicating a successful removal of the tumor. Patient experienced significant lower extremity pitting edema two months post pituitary surgery. An ultrasound conducted by the primary care physician ruled out blood clots, and the edema has since resolved. The clinician suggests the edema may have been related to post-surgical hormone imbalance. Patient was educated on signs and symptoms suggested to continue monitoring and to report if any symptoms recur.

The patient now follow-up with the endocrinologist at Norman Regional Hospital. Her physical examination shows regular heart rhythm, clear lungs, reflexes 2+, and absence of edema or abdominal pain. Notably, the patient has a history of osteopenia without fractures and PCOS, which necessitated ovarian wedge resection in the past for her willingness to become pregnant.

As per her first encounter due to her persistent elevated levels of IGF-1 the specialist opted to perform another brain MRI to rule out any new tumor growth or co-secretory tumor involving ACTH and growth hormone. Lab work was ordered for fasting morning labs for IGF-1 and growth hormone levels to track the levels of ACTH,cortisol,IGF-1. Fortunately, the MRI showed no evidence of abnormality with consistent homogeneous contrast enhancement. Her recent lab report demonstrated the endocrine hormone levels as shown in (Table:2).

**Table.2:- Lab reports,2025**

| Parameter | Result |
|---|---|
| Growth Hormone | 0.56 ng/mL |
| IGF-1 | 242 ng/mL |
| Serum Cortisol (24-hr) | 14.6 µg/24 hr |
| Serum ACTH | 40 pg/mL |
| TSH, Free T4 | Within the reference range |
| Prolactin, Estradiol, FSH, LH | Within the reference range |

During her follow-up her lab reports were discussed with an intention to consider Oral Glucose Tolerance Test (OGTT) if the levels of the growth hormone level increases in the future, and the patient was suggested to report back if any new symptoms arose. Follow up appointment was scheduled.

## 3. DISCUSSION

More than 90% of CD patients have pituitary adenomas. These tumors are typically smaller than those secreting GH or PRL; 80% to 90% are less than 10 m in m in diameter (2). CD is primarily treated with transsphenoidal surgery, though recurrence rates range from 10% to 30% over 10 years, necessitating long-term monitoring with biochemical tests and imaging (3). Mixed ACTH and GH-secreting pituitary adenomas, although rare, have been described in literatures, underscoring the need for dual hormone screening in atypical presentations (6,8).

This case demonstrates several diagnostic pitfalls. The initial workup relied on a single elevated UFC without a second confirmatory test, deviating from guideline recommendations. Initial unilateral adrenalectomy cured the adrenal disorder in this patient but failed to achieve sustained remission due to an undiagnosed pituitary ACTH source for which transsphenoidal pituitary tumor resection guided by IPSS was done- the gold standard for Cushing's disease.4 Furthermore, the initial normal but non-suppressed ACTH level of 29 pg/mL was a critical, albeit overlooked, clue pointing toward ACTH-dependent Cushing's disease. In retrospect, the adrenal adenomas identified were likely ACTH-driven hyperplasia and nodules, a known phenomenon in long-standing CD that can misleadingly suggest a primary adrenal etiology. Following transsphenoidal resection, the patient's serum cortisol level was 6.1 µg/dL, ACTH was 18 pg/mL, and IGF-1 was reported elevated; however, she exhibited no clinical signs of acromegaly, including jaw enlargement, enlarged hands/feet, or hyperhidrosis.

Management was guided by pharmacologic hormone monitoring (cortisol, ACTH, IGF-1), preventive annual MRIs, patient education for symptom identification, targeted diagnostics (fasting labs, OGTT), and supportive treatment of comorbidities (osteopenia, PCOS and transient post-surgical edema).

Clinician assessments confirm that the patient has achieved biochemical remission, with normalized cortisol and ACTH levels. While IGF-1 remains slightly elevated, it was not considered concerning. From the patient's perspective, symptoms like edema and hypercortisolism have resolved, and she reports satisfaction with her care. Her follow-up plan includes regular fasting morning labs (cortisol, ACTH, IGF-1, GH, prolactin), periodic assessment of bone mineral density to detect osteoporosis progression, detailed clinical evaluation for acromegalic features along with serial IGF-1 measurements, and annual MRIs for the next three years to monitor for recurrence. Beyond that, imaging will be done periodically based on her clinical status. If GH levels rise, an OGTT may be performed to rule out co-secretion. Ongoing follow-up appointments will focus on maintaining hormonal balance and catching any signs of recurrence early. This monitoring strategy is based on established guidelines, which indicate a 10–30% recurrence rate within 10 years(3). The patient's transient post-surgical edema is likely due to temporary HPA axis instability and is expected to resolve over time.

Histopathological studies support the co-localization of ACTH and GH in the same tumor cells, consistent with plurinominal adenomas (7). These tumors frequently co-express multiple hormonal markers and may drive from trans differentiation mechanisms through transcription factors such as Pit-1 and NeuroD1 (6). In addition, plurihormonality seems to predict a higher risk of tumor recurrence . While the patient's tumor was removed, there is a lack of histopathological data to confirm if the nature of the tumor was purely ACTH-producing or if it co-secretes other hormones like GH. The patient's current follow-up timeline and post-operative course have been described, but long-term follow-up data beyond a few months would have been helpful in assessing if any further complications arise. Long-term data would also allow for a more definitive conclusion regarding the patient's overall recovery and the impact of her treatment.

This case illustrates that presumed adrenal Cushing syndrome warrants confirmatory ACTH sampling and sensitive MRI evaluation when clinical suspicion remains high, to avoid delays in identifying a pituitary source. It also serves as a reminder to adhere to diagnostic guidelines, which call for multiple positive screening tests and careful interpretation of ACTH levels, even when they fall within the normal range.

## 4. CONCLUSION

This case provides evidence of the limitations of routine imaging including an MRI brain that did not demonstrate a pituitary lesion and the importance of inferior petrosal sinus sampling (IPSS) for localizing ACTH secretion when imaging does not provide a definitive diagnosis. The deviation from diagnostic guidelines for biochemistry, including reliance on a single urinary free cortisol (UFC) and failure to recognize that an ACTH level that is in the normal range does not provide sufficient evidence that a pituitary adenoma secreting ACTH can be excluded to arrive at a diagnosis earlier rather than later, was also impactful. The subsequent postoperative resection of the ACTH secreting pituitary microadenoma after successful localization leads to biochemical cure and symptom resolution, proving that at least in this patient, a stepwise approach using evidence-based guidelines proved useful in the clinical workup. Additionally, it also highlights the importance of going beyond first evaluations, remaining flexible around diagnostic consideration, and ensuring long-term support for patients beyond therapeutic measures even if the treatment provided is successful.

Furthermore, the incidental finding of persistently elevated IGF-1 postoperatively, raises suspicion of pituitary co-secretion syndromes, reminding clinicians to perform thorough hormonal evaluations with complex cases. This case not only reinforces the diagnostic value IPSS but highlights the value of a multi-disciplinary approach and long-term active follow-up approach to the management of endocrine disorders with overlapping and changing clinical presentations.

This case gives reasons as to why a routine imaging such as an MRI brain that fails to show a pituitary lesion and inferior petrosal sinus sampling (IPSS) are significant in the localization of ACTH secretion failed to deliver a definite diagnosis. The fact that the diagnostic guidelines were deviated in biochemistry, such as utilization of a single urinary free cortisol (UFC) and not considering that an ACTH level within normal range does not give adequate evidence that a pituitary adenoma secretion ACTH may be ruled out in order to make a diagnosis earlier than later were also effective. The following postoperative surgery to excise the ACTH secreting pituitary microadenoma following successful localization results in biochemical remission and symptom resolution, which demonstrates that at least in this case, a step-by-step approach and application of evidence-based guidelines are beneficial in the work up. Also, it emphasizes the need to go beyond the initial consideration, flexibility in the consideration of diagnosis, and long-term support of the patient after the therapeutic intervention even in the case of success of the treatment administered. In addition, the chance finding of persistently high IGF-1 after surgery, makes one apprehensive of pituitary co-secretion syndromes, in order to remind clinicians to conduct detailed hormonal assessments on complex cases. Besides underlining the diagnostic worth IPSS, this case demonstrates the importance of a multi-disciplinary approach, as well as the long-term active follow-up strategy to managing the endrocrine disorders with an overlapping and changing clinical appearance.

## 5. REFERENCES


1. Camacho P, ed. Atlas of Clinical Endocrinology and Metabolism. CRC Press; 2024:167-168.
2. Gardner D, ed. Greenspan's Basic and Clinical Endocrinology. 9th ed. McGraw-Hill; 2011.
3. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(8):2807-2831. doi:10.1210/jc.2015-1818
4. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: A guideline update. Lancet Diabetes Endocrinol. 2021;9(12):847-875. doi:10.1016/S2213-8587(21)00235-7
5. Nadel J, Couldwell WT. Management of water and sodium disturbances after transsphenoidal resection of pituitary tumors. Neurol India. 2020;68(Suppl 1):S101-S105. doi:10.4103/0028-3886.287679
6. Melmed S. Pathogenesis of pituitary tumors. Nat Rev Endocrinol. 2011;7(5):257-266.
7. Tahara S, Kurotani R, Ishii Y, et al. A case of Cushing's disease caused by pituitary adenoma producing adrenocorticotropic hormone and growth hormone concomitantly: Aberrant expression of transcription factors NeuroD1 and Pit-1 as a proposed mechanism. Mod Pathol. 2002;15(11):1102-1105.
8. Pawlikowski M, Kunert-Radek J, Radek M. Plurihormonality of pituitary adenomas in light of immunohistochemical studies. Endokrynol Pol. 2010;61(1):63