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CUSHING'S DISEASE IN A YOUNG ADULT WITH ADRENAL INCIDENTALOMA: A DIAGNOSTIC ODYSSEY THROUGH BIOCHEMICAL AND RADIOLOGICAL WORKUP

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ABSTRACT

Cushing's disease, resulting from ACTH-dependent hypercortisolism driven by a pituitary corticotroph adenoma, represents a diagnostically challenging endocrine disorder. We report the case of a 29-year-old male who presented with dyspnea and was found to have features of cortisol excess including hypertension, lower lid retraction, hyperpigmented knuckles, and abdominal striae. Biochemical evaluation confirmed autonomous cortisol hypersecretion: elevated baseline cortisol (34.38µg/dL), elevated ACTH (71.6 pg/mL), elevated 24-hour urinary free cortisol (300 µg/day), and failure of suppression on low-dose dexamethasone testing, with paradoxical suppression on high-dose testing (2.7 µg/dL), consistent with a pituitary source. Intriguingly, the MRI pituitary with plain and contrast sequences was reported as normal, raising the possibility of a microadenoma below imaging resolution. CT abdomen demonstrated mild right adrenal thickening (4.5 mm), likely reflecting secondary adrenal hyperplasia. The diagnostic workup was escalated to bilateral inferior petrosal sinus sampling (BIPSS) at a tertiary referral center, establishing the pituitary as the source of excess ACTH. This case underscores the critical role of stepwise biochemical confirmation in Cushing's disease, the limitations of MRI in detecting microadenomas, and the indispensable value of BIPSS in cases with inconclusive imaging.

KEYWORDS: Cushing's Disease, ACTH-Dependent Hypercortisolism, Dexamethasone Suppression Test, Bilateral Inferior Petrosal Sinus Sampling (BIPSS), Pituitary Microadenoma, Adrenal Hyperplasia, Urinary Free Cortisol.

INTRODUCTION

Cushing's syndrome encompasses a spectrum of clinical and metabolic consequences arising from prolonged exposure to supraphysiological glucocorticoid levels. Among its various etiologies, Cushing's disease — defined specifically as ACTH-dependent hypercortisolism secondary to a pituitary corticotroph adenoma — accounts for approximately 70–80% of all endogenous Cushing's syndrome cases in adults. The remaining cases include ectopic ACTH secretion (10–15%) and primary adrenal causes (15–20%).

The diagnostic pathway for Cushing's disease is inherently complex and requires a stepwise approach: first confirming endogenous hypercortisolism, then establishing ACTH-dependence, and finally localizing the source to the pituitary. This process is confounded by the fact that pituitary microadenomas — the most common cause — frequently escape detection on standard MRI, with imaging sensitivity reported at only 50–60% for lesions smaller than 6 mm. In such scenarios, bilateral inferior petrosal sinus sampling (BIPSS) becomes the definitive procedure for source localization.

We present this case to highlight the diagnostic challenge of Cushing's disease presenting with a normal pituitary MRI, the clinical and cardiac implications of chronic hypercortisolism in a young male, and the critical role of advanced sampling techniques in confirming the pituitary etiology.

CASE PRESENTATION

A 29-year-old male farmer presented to the Department of General Medicine, Tirunelveli Medical College and Hospital, with a four-day history of progressive dyspnea on exertion. There was no prior history of diabetes mellitus, hypertension, tuberculosis, or malignancy documented prior to this admission.

Clinical Examination

On admission, the patient was conscious and oriented. General examination revealed pallor and tachypnea, without icterus, clubbing, cyanosis, lymphadenopathy, or pedal edema. Critically, several features of chronic cortisol excess were noted on careful physical examination:

- Lower lid retraction — a recognized ocular manifestation of orbitopathy in the context of metabolic endocrinopathy
- Hyperpigmented knuckles — suggestive of elevated ACTH levels driving melanocortin receptor stimulation
- Abdominal striae — a hallmark cutaneous feature of Cushing's syndrome reflecting protein catabolism and skin fragility

Cardiovascular examination was pertinent: the echocardiogram demonstrated dilated left atrium and left ventricle, mild tricuspid regurgitation (TR), moderate mitral regurgitation (MR), mild global hypokinesia of the left ventricle, preserved ejection fraction of 50%, mild left ventricular systolic dysfunction (LVSD), Grade II left ventricular diastolic dysfunction (LVDD), and concentric left ventricular hypertrophy (LVH) — a pattern consistent with hypertensive and glucocorticoid-induced cardiomyopathy.

Blood Pressure Monitoring

Serial blood pressure measurements documented sustained, refractory hypertension across all time points over a six-day period:

Date	8:00 AM	2:00 PM	8:00 PM
22/09/2024	180/120	180/120	190/120
23/09/2024	170/120	170/120	180/120
24/09/2024	180/110	170/110	170/110
25/09/2024	170/120	160/110	160/100
26/09/2024	160/100	140/100	140/100
27/09/2024	150/110	140/100	140/80

INVESTIGATIONS

1. Routine Hematological and Biochemical Profile

Parameter	Admission Value	Follow-up Value
Total Leukocyte Count (/µL)	13,500	7,100
Hemoglobin (g/dL)	8.9	8.8
Blood Urea (mg/dL)	44.0	50.3
Serum Creatinine (mg/dL)	1.7	1.4
Random Blood Sugar (mg/dL)	132	144
Fasting Blood Sugar (mg/dL)	135	—
Post-prandial Blood Sugar (mg/dL)	159	—
HbA1c (%)	6.3	—
Serum Na^+ (mEq/L)	139	139
Serum K^+ (mEq/L)	4.2	4.0
Liver Function Tests	Normal	Normal
Lipid Profile	Normal	Normal
Thyroid Function Tests	Normal	Normal
Coagulation Profile	Normal	Normal

Peripheral smear revealed microcytic, hypochromic anemia, consistent with the chronic inflammatory and catabolic state of Cushing's syndrome.

2. Hormonal and Biochemical Evaluation for Hypercortisolism

The step-wise hormonal workup was pivotal in confirming Cushing's disease:

Investigation	Patient's Value	Reference Range
Baseline Serum Cortisol (µg/dL)	34.38	6.7 – 22.6
Baseline Plasma ACTH (pg/mL)	71.6	< 46
24-Hour Urinary Free Cortisol (µg/day)	300	4.3 – 176
Overnight DST — Post-Dexamethasone Cortisol (µg/dL)	25.54	6.7 – 22.6
Low-Dose DST — Post-Dexamethasone Cortisol (µg/dL)	21.8	6.7 – 22.6
High-Dose DST — Post-Dexamethasone Cortisol (µg/dL)	2.7	6.7 – 22.6

The elevated baseline cortisol, elevated ACTH, markedly elevated 24-hour urinary free cortisol (UFC), and failure of suppression on both overnight and low-dose dexamethasone suppression tests (DST) confirmed

endogenous, ACTH-dependent hypercortisolism. The paradoxical suppression on high-dose DST (≥50% suppression from baseline) strongly supported a pituitary rather than ectopic source.

3. Radiological Investigations

- MRI Pituitary (Plain + Contrast): Reported as a normal study — no discrete pituitary adenoma identified on standard sequences. This finding, while potentially reassuring, does not exclude a microadenoma below the resolution threshold of conventional MRI.
- CT Abdomen with Adrenals: Mild bilateral adrenal thickening noted, with maximum thickening of 4.5 mm in the right adrenal gland — consistent with secondary adrenal hyperplasia driven by chronic ACTH stimulation rather than a primary adrenal neoplasm.
- USG Abdomen and Pelvis: Grade I medical renal disease (MRD). No solid organ masses or vascular abnormalities detected. Renal artery Doppler showed no evidence of direct renal artery stenosis.

4. Cardiac Evaluation

Echocardiography revealed a constellation of cardiac changes attributable to the combined effects of hypertension and chronic glucocorticoid excess: dilated LA and LV, mild global LV hypokinesia, EF 50%, mild LVSD, Grade II LVDD, concentric LVH, mild TR, and moderate MR. These findings mandated cardiology co-management and carried implications for perioperative risk stratification should surgical intervention be pursued.

DIFFERENTIAL DIAGNOSIS

The following differential diagnoses were systematically evaluated:

- Cushing's Disease (Pituitary ACTH-Secreting Adenoma): Primary diagnosis. Supported by elevated ACTH, failure of low-dose DST, suppression on high-dose DST, and absence of adrenal mass on CT. The normal MRI pituitary does not exclude a microadenoma; BIPSS was pursued for definitive source localization.
- Ectopic ACTH Syndrome: Considered given the elevated ACTH and normal pituitary MRI. However, ectopic sources typically demonstrate failure of suppression even on high-dose DST and are associated with more rapid onset and profound hypokalemia — neither of which was prominently present here. BIPSS lateralization to the pituitary excluded this diagnosis.
- Primary Adrenal Cushing's Syndrome (Adrenal Adenoma/Hyperplasia): Excluded by the elevated ACTH level (ACTH is suppressed in primary adrenal causes) and by CT findings showing only mild adrenal thickening rather than a discrete adrenal adenoma.
- Pseudo-Cushing's States (Alcohol-Related or Depression-Induced): Excluded by the absence of alcoholism, major psychiatric disease, or normalization of cortisol following a structured evaluation period.

DISCUSSION

This case of Cushing's disease in a 29-year-old male illustrates the diagnostic complexity that arises when clinical and biochemical evidence strongly supports a pituitary etiology, yet standard neuroimaging is unrevealing. It highlights three critical areas: the stepwise biochemical approach to confirming and localizing hypercortisolism, the cardiac and metabolic burden of chronic cortisol excess in a young patient, and the indispensable role of BIPSS in MRI-negative cases.

1. Biochemical Confirmation and Source Localization

The diagnostic algorithm for Cushing's disease follows a sequential logic: (a) confirm hypercortisolism, (b) establish ACTH-dependence, and (c) localize the source. In this patient, all three steps were fulfilled.

Hypercortisolism was confirmed by three concordant tests: elevated baseline serum cortisol, markedly elevated 24-hour UFC (300 µg/day, nearly twice the upper limit of normal), and failure of overnight and low-dose DST. Elevated ACTH (71.6 pg/mL) established ACTH-dependence, thereby directing attention toward either a pituitary or ectopic source.

The high-dose DST result was particularly instructive. The principle of high-dose DST rests on the observation that pituitary corticotroph adenomas retain partial sensitivity to glucocorticoid feedback, and thus demonstrate ≥50% suppression of cortisol from baseline when challenged with 8 mg dexamethasone. Ectopic ACTH sources, by contrast, are entirely autonomous. The suppression to 2.7 µg/dL in this patient (a >90% reduction from baseline cortisol) is a robust indicator of pituitary origin, with specificity exceeding 90% in most series.

When MRI pituitary failed to identify a discrete adenoma, BIPSS was performed at a tertiary referral center (RGGGH, Chennai). BIPSS remains the gold-standard procedure for distinguishing pituitary from ectopic ACTH secretion, with a diagnostic sensitivity exceeding 95% and specificity approaching 100%. A central-to-peripheral ACTH gradient of ≥2:1 at baseline or ≥3:1 after CRH stimulation confirms pituitary origin. The results in this patient confirmed pituitary ACTH hypersecretion, allowing appropriate neurosurgical planning.

2. Normal Pituitary MRI in Cushing's Disease

The phenomenon of a biochemically confirmed Cushing's disease with a normal pituitary MRI is well documented and occurs in approximately 30–50% of cases, particularly when the adenoma is less than 6 mm in size. Standard MRI sequences may miss microadenomas due to their small size, isointense

appearance on T1-weighted images, and location within the gland parenchyma.

Dynamic contrast-enhanced MRI with spoiled gradient-recalled echo (SPGR) or 3D VIBE sequences improve detection sensitivity and were recommended as the next step in this patient's imaging workup. The mild adrenal thickening observed on CT (4.5 mm, right-sided) is not indicative of autonomous adrenal disease but rather reflects the bilateral adrenocortical hyperplasia that invariably accompanies chronic ACTH stimulation, further supporting the central etiology.

3. Cardiovascular Burden of Cushing's Disease

The echocardiographic findings in this patient — concentric LVH, diastolic dysfunction, mild global hypokinesia, and preserved-to-mildly-reduced ejection fraction — represent the cardiovascular signature of chronic glucocorticoid excess. Glucocorticoids increase cardiac output, promote sodium retention (via mineralocorticoid receptor cross-reactivity), and directly induce myocardial hypertrophy and fibrosis through glucocorticoid receptor-mediated pathways.

Sustained, treatment-refractory hypertension (as documented in the serial BP chart, with values ranging from 180/120 to 190/120 mmHg) further compounds the cardiac risk. The mild tricuspid and moderate mitral regurgitation likely represent functional valvular pathology secondary to volume overload and ventricular remodeling. Cardiovascular risk reduction through curative treatment of hypercortisolism is therefore not merely symptomatic but prognostically essential.

4. Metabolic Consequences

The HbA1c of 6.3% (pre-diabetic range), elevated FBS (135 mg/dL), and PPBS (159 mg/dL) reflect glucocorticoid-induced glucose dysregulation, mediated by hepatic gluconeogenesis stimulation, peripheral insulin resistance, and suppression of pancreatic beta-cell function. Normoglycemia is expected to improve significantly following curative treatment of hypercortisolism. The microcytic, hypochromic anemia may reflect the catabolic milieu and possible iron deficiency in the context of chronic hypertensive cardiomyopathy and poor nutritional intake.

CONCLUSION

This case of Cushing's disease in a young adult underscores the importance of adhering rigorously to the stepwise biochemical algorithm even when clinical suspicion is high, as each test provides an incremental layer of diagnostic certainty. The normal pituitary MRI in this case is a crucial reminder that a negative imaging result does not exclude a pituitary adenoma and that BIPSS remains the non-negotiable gold standard for source localization in such scenarios.

The cardiac findings in this patient serve as a sobering reminder of the systemic devastation wrought by untreated hypercortisolism, including hypertensive cardiomyopathy, diastolic dysfunction, and functional valvular disease. Early diagnosis and curative surgical resection (transsphenoidal adenomectomy) offer the greatest prospect for remission of hypercortisolism and reversal of its cardiovascular, metabolic, and musculoskeletal sequelae.

Clinicians encountering young adults with refractory hypertension, unexplained cardiomyopathy, or subtle clinical stigmata of cortisol excess should maintain a high index of suspicion for Cushing's disease, initiating prompt hormonal evaluation rather than attributing the presentation to more common primary diagnoses.

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