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"CUSHING'S DISEASE CHALLENGES IN DIAGNOSIS: WHEN THE CHRONOLOGY OF LABORATORY TESTS NEEDS TO BE FOLLOWED A CASE REPORT AND MINI REVIEW "

DOENÇA DE CUSHING ARMADILHAS NO DIAGNÓSTICO: QUANDO A CRONOLOGIA DOS TESTES LABORATORIAIS NECESSITA SER SEGUIDA UM RELATO DE CASO E MINI REVISÃO

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Abstract: Cushing's disease (CD) is the leading cause of endogenous Cushing's syndrome (CS), resulting from excessive adrenocorticotropic hormone (ACTH) secretion by pituitary adenomas, leading to chronic hypercortisolism and its multiple systemic repercussions. Despite being well defined from a pathophysiological standpoint, its diagnosis remains challenging due to the insidious clinical presentation and overlap with prevalent conditions such as obesity, type 2 diabetes mellitus, and metabolic syndrome. This study aims to highlight the diagnostic pitfalls of CD, emphasizing the importance of proper sequencing and interpretation of laboratory tests.

We report the case of a 53-year-old female patient with long-standing type 2 diabetes mellitus and multiple microvascular and macrovascular complications, associated with persistently inadequate glycemic control. On physical examination, she presented classic signs of hypercortisolism, including central obesity, moon facies, abdominal striae, and a dorsocervical fat pad. Initial investigation excluded an exogenous cause. Laboratory evaluation confirmed hypercortisolism, evidenced by elevated serum cortisol, late-night salivary cortisol, and urinary free cortisol levels, along with failure to suppress on the dexamethasone suppression test. Elevated ACTH levels characterized an ACTH-dependent condition, consistent with CD.

This case illustrates the importance of a structured diagnostic approach based on biochemical confirmation of hypercortisolism prior to imaging studies, thereby avoiding misinterpretation due to incidentalomas. It also highlights the need to consider the limitations of laboratory tests, particularly in patients with comorbidities such as chronic kidney disease. In conclusion, CD should be suspected in patients with difficult-to-control metabolic syndrome and suggestive clinical features. Early diagnosis, based on careful clinical evaluation and an appropriate sequence of tests, is essential to reduce morbidity, guide appropriate treatment, and improve patient prognosis and quality of life.

Keywords: Cushing disease; Dexamethasone suppression test; Late-night salivary cortisol; Urinary free cortisol.

Resumo: A doença de Cushing (DC) é a principal causa de síndrome de Cushing (SC) endógena, resultante da secreção excessiva de ACTH por adenomas hipofisários, levando ao hipercortisolismo crônico e suas múltiplas repercussões sistêmicas. Apesar de bem definida fisiopatologicamente, seu diagnóstico permanece desafiador devido à apresentação clínica insidiosa e à sobreposição com condições prevalentes, como obesidade, diabetes mellitus tipo 2 e síndrome metabólica. Este estudo tem como objetivo destacar as armadilhas diagnósticas da DC, enfatizando a importância da sequência e da interpretação adequada dos testes laboratoriais. Relata-se o caso de uma paciente de 53 anos com diabetes mellitus tipo 2 de longa data e múltiplas complicações micro e macrovasculares, associadas a controle glicêmico persistentemente inadequado. Ao exame físico, apresentava sinais clássicos de hipercortisolismo, como obesidade central, fácies em lua cheia, estrias abdominais e giba dorsocervical. A investigação inicial excluiu a causa exógena. A avaliação laboratorial confirmou hipercortisolismo, evidenciado por níveis elevados de cortisol sérico, salivar noturno e urinário, além de ausência de supressão no teste com dexametasona. A dosagem de ACTH elevada caracterizou um quadro ACTH-dependente, compatível com DC. O caso ilustra a importância da abordagem diagnóstica estruturada, baseada na confirmação bioquímica do hipercortisolismo antes da realização de exames de imagem, evitando interpretações equivocadas decorrentes de incidentalomas. Destaca-se também a necessidade de considerar limitações dos testes laboratoriais, especialmente em pacientes com comorbidades como doença renal crônica. Conclui-se que a DC deve ser suspeitada em pacientes com síndrome metabólica de difícil controle e manifestações clínicas sugestivas. O diagnóstico precoce, baseado em avaliação clínica criteriosa e sequência adequada de testes, é fundamental para reduzir a morbidade, orientar o tratamento adequado e melhorar o prognóstico e a qualidade de vida dos pacientes.

Descritores: Doença de Cushing; Teste supressão da dexametasona; Cortisol salivar à meia noite; Cortisol livre urinário.

INTRODUCTION

Cushing's disease (CD) is the most common cause of endogenous Cushing's syndrome (CS) and results from an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. This condition leads to chronic hypercortisolism through persistent

stimulation of the adrenal cortex, culminating in increased cortisol production and systemic metabolic dysregulation[1].

From a pathophysiological standpoint, the disease arises from dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, in which autonomous ACTH secretion by a corticotroph adenoma promotes continuous adrenal stimulation and excessive cortisol production, independent of physiological negative feedback mechanisms. As a consequence, the circadian rhythm of cortisol secretion is disrupted, with persistently elevated levels throughout the day — one of the most characteristic findings of the disease[2].

Despite being well established conceptually, CD remains frequently underdiagnosed or late-diagnosed. This is largely attributable to the insidious nature of its clinical manifestations, which often overlap with highly prevalent conditions such as obesity, metabolic syndrome, diabetes mellitus, depression, and alcoholism. Furthermore, pseudo-Cushing states, the use of interfering medications, and cyclic forms of the disease represent important sources of diagnostic error[3].

In this context, the diagnosis of CD requires a systematic approach based on laboratory tests that assess different aspects of cortisol physiology, including circadian rhythm, overall production, and the integrity of HPA axis feedback. However, beyond test selection, correct interpretation and, most importantly, adherence to the appropriate chronological sequence in which they are performed are critical determinants of diagnostic accuracy[1,3].

Given these limitations, initiating the investigation with imaging studies may lead to diagnostic misinterpretation, particularly in view of the high prevalence of pituitary and adrenal incidentalomas in the general population. Therefore, this case report aims to highlight the main diagnostic pitfalls in Cushing's disease, emphasizing proper test sequencing and the chronological interpretation of laboratory findings as essential elements for accurate diagnosis and appropriate clinical management.

CASE REPORT

A 53-year-old female patient with a diagnosis of type 2 diabetes mellitus (T2DM), first established at the age of 25 during pregnancy, has been on insulin therapy since the

age of 43. She presents multiple diabetes-related target organ complications, including diabetic retinopathy, heart failure with preserved ejection fraction (HFpEF; EF: 54.9%), chronic kidney disease (CKD) stage G3bA3, and diabetic neuropathy. Her past medical history is also notable for class II obesity (BMI: 35.1 kg/m²), hypothyroidism, systemic arterial hypertension, dyslipidemia, peripheral arterial disease, and a prior episode of deep vein thrombosis.

The patient was referred by the Cardiology Department to the Endocrinology outpatient clinic at Hospital Universitário Evangélico Mackenzie for optimization of the metabolic management of T2DM, given the multiplicity of complications. On physical examination, a phenotype strongly suggestive of hypercortisolism was identified, characterized by central obesity, abdominal striae, moon facies, and dorsocervical fat accumulation (buffalo hump). Based on these findings, an investigation for Cushing's syndrome was initiated. Exogenous etiology was promptly excluded, as the patient reported no prior glucocorticoid use.

Initial laboratory evaluation revealed chronically refractory glycemic control, with glycated hemoglobin (HbA1c) values ranging from 11.3% to 12.9%. Additionally, a progressive decline in renal function was documented: the estimated glomerular filtration rate (eGFR) was 44.86 mL/min/1.73m², accompanied by a marked increase in the urinary albumin-to-creatinine ratio (UACR), which progressed from 710 mg/g to 5,972 mg/g, and 24-hour proteinuria of 5,099 mg, consistent with nephrotic-range proteinuria.

Evaluation of the hypothalamic–pituitary–adrenal (HPA) axis confirmed hypercortisolism, with the following findings: morning basal serum cortisol of 30.16 µg/dL, morning salivary cortisol of 3.250 µg/dL, post-dexamethasone suppression serum cortisol of 21.12 µg/dL, midnight serum cortisol of 28.87 µg/dL, and 24-hour urinary free cortisol of 545 µg/24h. Subsequent measurement of adrenocorticotropic hormone (ACTH) revealed an elevated level of 126 pg/mL, indicating an ACTH-dependent etiology.

Based on clinical and laboratory correlation, a diagnosis of Cushing's disease was established. For etiological characterization and assessment of complications

secondary to chronic hypercortisolism, pituitary magnetic resonance imaging (MRI) and bone densitometry were requested, respectively.

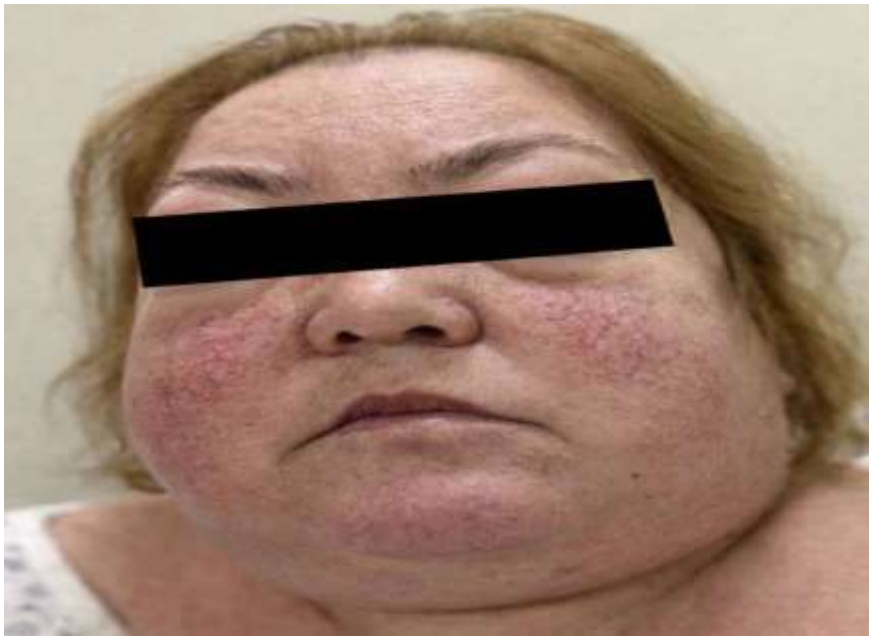

Figure 1: Moon facies associated with periorbital edema, facial plethora, and telangiectasias, clinical findings suggestive of hypercortisolism.

Table 1: Laboratory biochemical analysis of the patient.

Laboratory Test (Unit of Measurement)	**Current Result**	**Previus Results**	**Reference Range**
Glomerular Filtration Rate (mL/min/1,73 m²)	44	36 → 48	≥ 90
Albuminuria (mg/g)	5099	710 → 5972	< 30
Glycated Hemoglobin (%)	12,40	11,3 → 12,9	< 7 in patients with DM
Post-Dexamethasone Cortisol (µg/dL)	21,12	—	≤ 1.8
Morning Salivary Cortisol (µg/dL)	3,250	—	< 0,736
24h -Hour Urinary Free Cortisol (µg/24h)	545	509	58,0 to 403,0

Table 1: Laboratory biochemical analysis of the patient.

Serum Cortisol (µg/dL)	28,87 (collected at 00h)	30,16 (collected at 09h)	6,70 to 22,60 (morning collection)
ACTH (pg/mL)	126	—	< 46

DISCUSSION: **Clinical, Laboratory, and Imaging Diagnosis**

Clinical Presentation

Patients with Cushing's disease present characteristic clinical manifestations resulting from prolonged exposure to excess cortisol. These include central obesity, moon facies, skin thinning, proximal muscle weakness, arterial hypertension, glucose intolerance or diabetes mellitus and neuropsychiatric symptoms. These findings may be accompanied by more specific signs — including wide violaceous striae, early-onset osteoporosis, hypogonadism, and menstrual irregularities — which further support the clinical diagnosis[2].

Despite these relatively distinctive features, diagnosis is frequently delayed, as many manifestations develop insidiously and overlap with more common conditions, such as obesity and metabolic syndrome[2,3].

Therefore, biochemical investigation should be pursued in patients with suggestive clinical findings. Prior to biochemical evaluation, exogenous glucocorticoid use must be excluded, as it remains the most frequent cause of hypercortisolism; this includes oral, injectable, inhaled, intra-articular, topical, and ophthalmic formulations[1].

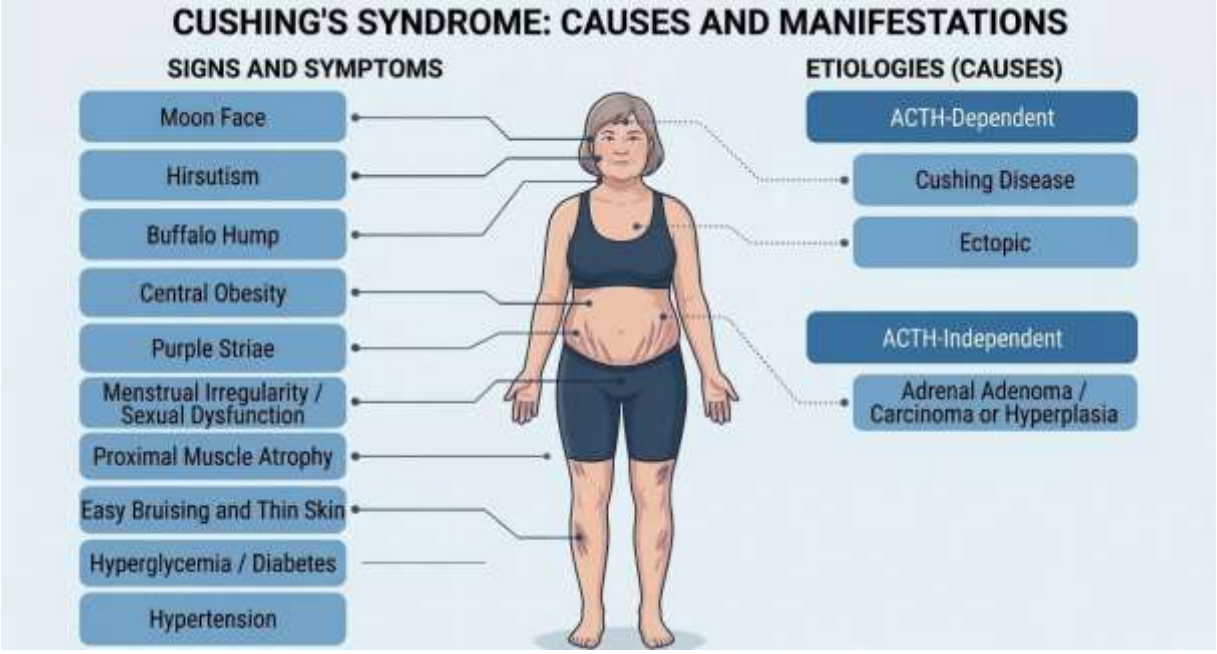

Figure 1. Causes and Manifestations of Cushing's Syndrome.*Adapted from: Nieman, L.K. et al., 2025. (Ref. No. 6).*

Laboratory Evaluation

Laboratory evaluation represents the next step following a thorough medical history and complete physical examination. A history of obesity, depression, and alcohol use is particularly relevant in differentiating true Cushing's syndrome from pseudo-Cushing states[3]. The diagnosis of Cushing's syndrome relies primarily on biochemical confirmation of hypercortisolism and assessment of cortisol secretion patterns. Exogenous glucocorticoid use — whether oral, injectable, inhaled, intra-articular, or topical, including cutaneous and hair-care formulations — must be carefully excluded[4]. Additionally, medications that increase corticosteroid-binding globulin (CBG) levels or induce CYP3A4 activity may yield false-positive results. Cyclical Cushing's syndrome may further complicate the interpretation of biochemical findings[4]. Notably, the "hook effect" — a well-recognized immunoassay artifact in which markedly elevated hormone concentrations paradoxically produce falsely low results due to antibody saturation — has not been reported in corticotroph adenomas, as these tumors rarely attain sufficient size to generate exceptionally high hormone concentrations[4,5]. These considerations underscore the importance of performing three established first-line screening tests for the accurate diagnosis of Cushing's syndrome, which remains a complex and diagnostically challenging condition[3–6].

- **Late-night salivary cortisol (LNSC):** a minimum of two measurements is recommended, particularly when the initial result is inconclusive.
- **24-hour urinary free cortisol (UFC):** at least two collections should be obtained in the setting of diagnostic uncertainty.
- **1 mg overnight dexamethasone suppression test (DST).**

These tests evaluate distinct aspects of cortisol physiology and must be interpreted with caution, taking into account their inherent limitations and potential sources of interference[6,7].

Late-Night Salivary Cortisol (LNSC)

Late-night salivary cortisol assesses the loss of the circadian nadir of cortisol secretion, a hallmark feature of hypercortisolism. Multiple measurements are generally recommended to enhance diagnostic accuracy.

Protocol: Two to three samples are collected at the patient's habitual bedtime (approximately midnight).

Clinical utility: This method demonstrates high sensitivity and specificity, and is particularly valuable in the evaluation of cyclic Cushing's syndrome and in longitudinal clinical follow-up.

Limitations: Its use should be avoided in shift workers owing to disruption of the circadian rhythm. Tandem mass spectrometry-based assays demonstrate superior analytical sensitivity relative to immunoassays, albeit with a marginal reduction in specificity[2,3,8].

24- Hour Urinary Free Cortisol (UFC)

Twenty-four-hour urinary free cortisol quantifies global hypercortisolism by measuring the excretion of biologically active cortisol over a complete 24-hour period.

Protocol: Two to three collections are recommended owing to intraindividual variability in cortisol secretion.

Advantages: This method is independent of corticosteroid-binding globulin (CBG) fluctuations and does not require synchronization with medication administration.

Limitations: UFC demonstrates lower sensitivity relative to the dexamethasone suppression test (DST) and late-night salivary cortisol (LNSC). Its use is not recommended in patients with significant renal impairment (creatinine clearance <60 mL/min) or polyuria (>5 L/day), as these conditions may directly interfere with urinary cortisol excretion[5,7].

Dexamethasone Suppression Test (DST)

The dexamethasone suppression test evaluates the integrity of the hypothalamic-pituitary-adrenal (HPA) axis glucocorticoid negative feedback mechanism. In healthy individuals, dexamethasone suppresses adrenocorticotropic hormone (ACTH) secretion and consequently reduces serum cortisol levels. In patients with Cushing's syndrome, this suppression is characteristically inadequate[8,9].

Protocol: A single oral dose of 1 mg dexamethasone is administered between 11 PM and midnight, with serum cortisol measurement performed at 8 AM the following morning.

Reference value: A serum cortisol level below 1.8 µg/dL (50 nmol/L) indicates a normal suppression response and confers a high negative predictive value for Cushing's syndrome. Values exceeding 3–5 µg/dL are more indicative of overt hypercortisolism, particularly in the context of adrenal incidentalomas[5,7,8].

Advantages: The DST demonstrates high sensitivity and is regarded as the most sensitive first-line screening test for Cushing's syndrome.

Limitations:

- **False-positive results** may arise from dexamethasone malabsorption, concomitant use of CYP3A4 enzyme inducers (e.g., phenobarbital, carbamazepine), or conditions associated with elevated corticosteroid-binding globulin (CBG) levels, such as pregnancy and exogenous estrogen therapy.
- **False-negative results** may occur with the use of dexamethasone metabolism inhibitors (e.g., fluoxetine, diltiazem) or in states of reduced CBG levels (e.g., nephrotic syndrome). Diagnostic sensitivity is further reduced in obese patients and those with type 2 diabetes mellitus[,9,10].

All first-line diagnostic tests for Cushing's syndrome demonstrate high sensitivity and specificity. Among these, the DST yields the highest sensitivity, whereas 24-hour UFC exhibits comparatively lower sensitivity. The specificity of all first-line screening tests appears to be broadly comparable[8]. Notably, late-night salivary cortisol (LNSC) represents the diagnostic test of choice in patients with suspected Cushing's disease, particularly in the presence of chronic kidney disease (CKD)[11].

TREATMENT

Transsphenoidal resection of the ACTH-secreting pituitary adenoma represents the gold-standard treatment for Cushing's disease. This approach achieves biochemical remission and resolution of hypercortisolism in the majority of patients. The endoscopic endonasal approach is widely employed, affording superior surgical visualization and reduced postoperative morbidity. Surgical outcomes are closely dependent on the expertise of the multidisciplinary team, with complete tumor resection constituting the primary determinant of remission[2,14].

MEDICAL THERAPY

Medical therapy is indicated for patients who are not surgical candidates, present with persistent or recurrent disease, or require preoperative cortisol control[11]. The primary therapeutic goal is to normalize cortisol levels, ameliorate metabolic complications, and reduce overall disease burden. Combination therapy may be employed when monotherapy proves insufficient[1,16,17]. Additional therapeutic modalities include radiotherapy — which is characterized by a slow onset of action — and bilateral adrenalectomy, the latter providing rapid cortisol control but necessitating lifelong hormonal replacement therapy and carrying a risk of corticotroph tumor progression (Nelson's syndrome)[3,17,18].

Tabela 2: Pharmacological Treatment of Cushing's Disease

Class / Drug	Mechanism of Action	Administration	Clinical Consideration	Main Adverse Effects
Esteroidogenesis Inhibitors				
Metyrapone	Inhibits 11β-hydroxylase (↓ cortisol)	Oral	Rapid action; useful in severe hypercortisolism; may worsen hyperandrogenism	Gastrointestinal (GI) Symptoms, hirsutism, hypertension, hypokalemia, adrenal insufficiency

Tabela 2: Pharmacological Treatment of Cushing's Disease

Osilodrostat	Inhibits 11β-hydroxylase	Oral	Potent; requires monitoring of cortisol and QTc	Nausea, headache, adrenal insufficiency, ↑ QTc
Cetoconazol	Inhibits multiple CYP450	Oral	Risk of hepatotoxicity; avoid in liver disease	Hepatotoxicity, male hypogonadism, ↑transaminases, ↑ QTc
Levocetoconazol	Inhibits steroidogenesis (CYP3A4)	Oral	Possibly lower hepatotoxicity risk; monitor liver function	GI symptoms, ↑ transaminases, possible ↑ QTc
Mitotano	Direct adrenolytic action	Oral	Slow onset, requires therapeutic drug monitoring; induces adrenal insufficiency	GI symptoms, CNS effects, dyslipidemia, teratogenicity
Etomidato	Inhibits 11β-hydroxylase	Intravenous	Indicated in emergencies; restricted to intensive care settings	Sedation, requires continuous monitoring
ACTH Secretion Inhibitors				
Cabergoline	Dopamine agonist (↓ ACTH)	Oral	Best response in mild cases; possible loss of efficacy over time	GI symptoms, dizziness, impulse control disorders
Pasireotide	Somatostatin analogue	Subcutaneous	May worsen glycemic control; requires monitoring	Hyperglycemia, diarrhea, nausea, cholelithiasis
Pasireotide LAR	Somatostatin analog (long-acting)	Intramuscular	Better adherence (monthly use); similar metabolic effects	Similar to standard formulation
Antagonista do receptor de glicocorticoide				
Mifepristone	Blocks glucocorticoid receptor	Oral	Useful in glycemic control dysregulation; clinical monitoring required (cortisol level unreliable)	Hypokalemia, edema, endometrial thickening, nausea

Adapted from:*Fleseriu M,et al., 2021(Ref.Nº1), Nieman, L.K. et al., 2025.(Ref.Nº 6).*

REMISSION AND RECURRENCE

Remission is defined by recovery of the hypothalamic-pituitary-adrenal (HPA) axis following surgical intervention, with biochemical criteria established as a serum cortisol level below 5 µg/dL within the first postoperative week, although some literature advocates a stricter threshold of less than 1.8 µg/dL[8,5,19]. Recurrence may manifest as a late event, with progressive elevation of cortisol levels over weeks to months, accompanied by the reappearance of clinical features — including weight gain, insomnia, and arterial hypertension — alongside biochemical alterations. Late-night salivary cortisol (LNSC) demonstrates superior sensitivity relative to 24-hour urinary free cortisol (UFC) for the early detection of recurrence. Even following confirmed remission, previously acquired comorbidities may persist and warrant continued clinical surveillance[20].

COMPLICATIONS AND COMORBIDITIES

Cushing syndrome is associated with multiple systemic complications that significantly contribute to increased morbidity and mortality. A hypercoagulable state is commonly observed, leading to an elevated risk of venous thromboembolism. Additionally, patients exhibit increased cardiovascular risk, often in association with obesity, type 2 diabetes mellitus, and dyslipidemia[5,21].

In the musculoskeletal system, patients may develop metabolic bone disease characterized by reduced bone mineral density and an increased incidence of fractures, particularly vertebral fractures. Growth hormone (GH) deficiency is relatively common following treatment, especially in cases of central etiology. GH replacement therapy may offer benefits such as improved body composition, increased bone mineral density, and enhanced quality of life; however, it may adversely affect glycemic control [9,10,22].

DIFFERENTIATION BETWEEN PITUITARY AND ECTOPIC SOURCES

When the source of adrenocorticotropic hormone (ACTH) excess remains indeterminate, inferior petrosal sinus sampling (IPSS) is regarded as the gold standard for etiological differentiation. Upon confirmation of ectopic ACTH secretion, further diagnostic evaluation should include thoracic computed tomography (CT), abdominal CT or magnetic resonance imaging (MRI), and positron emission tomography–computed tomography (PET-CT) in selected cases. The neoplasms most commonly implicated in this context comprise small-cell lung carcinoma, bronchial neuroendocrine tumors, and pancreatic neuroendocrine tumors [22,23].

CONCLUSION

This case report underscores the importance of maintaining a high index of clinical suspicion for Cushing’s syndrome, particularly Cushing’s disease, in patients presenting with difficult-to-control metabolic syndrome. Although conditions such as type 2 diabetes mellitus, obesity, hypertension, and dyslipidemia are highly prevalent, cases characterized by treatment resistance and rapid progression of target-organ damage should prompt consideration of secondary etiologies.

In this context, a comprehensive clinical assessment, combined with strict adherence to a structured diagnostic algorithm, is essential for accurate diagnosis. The systematic approach to the investigative process—from initial screening tests to definitive etiological confirmation of adrenocorticotropic hormone (ACTH)-dependent hypercortisolism—was crucial in elucidating the present case.

Despite its rarity, Cushing's disease carries substantial clinical significance and poses considerable management challenges. Early diagnosis, timely implementation of appropriate therapeutic interventions, surgical management when indicated, and individualized long-term follow-up are critical to reducing morbidity and improving patient quality of life.

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