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Adrenocorticotropic Hormon-Secreting Pheochromocytoma: A Rare Cause of Cushing's Syndrome

Adrenokortikotropik Hormon Salgılayan Feokromositoma: Cushing Sendromunun Nadir Bir Nedeni

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Abstract

Pheochromocytoma is a rare cause of ectopic Cushing's syndrome and presents a challenge to the clinician in the diagnosis and treatment. In this study, a rare case of adrenocorticotropic hormone-producing pheochromocytoma is presented. A 55-years-old man with the symptoms of hypercortisolism, multidrug-resistant hypertension, and an adrenal mass is presented. The laboratory results were consistent with hypercortisolism, high plasma adrenocorticotropic hormone, high 24-hour urine metanephrine and normetanephrine and severe hypokalemia. Abdominal computerized tomography showed a 3-cm non-adenoma left adrenal mass. After preoperative management, left adrenalectomy was performed. A histopathological examination revealed a 2.5 cm pheochromocytoma with focal positivity for adrenocorticotropic hormone. The patient was discharged with full recovery under hydrocortisone replacement therapy. Furthermore, six weeks after the operation, 24-hour urinary excretion of metanephrine and normetanephrine was within normal ranges. In conclusion, an adrenocorticotropic hormone-producing pheochromocytoma should be considered in patients with clinical manifestations of ectopic Cushing's syndrome and adrenal mass.

Keywords: Ectopic Cushing's syndrome; pheochromocytoma; ACTH staining

Özet

Feokromositoma ektopik Cushing senrfomu'nun nadir bir nedenidir, tanı ve tedavi aşamalarında klinisyen için güçlük oluşturmaktadır. Çalışmamızda, nadir görülen adrenokortikotropik hormon salgılayan feokromositomalı bir hastanın sunulması amaçlanmıştır. Elli beş yaşında erkek hasta; hiperkortizolizm semptomları, dirençli hipertansiyon ve adrenal kitle nedeniyle kliniğimize kabul edildi. Laboratuvar bulguları hiperkortizolizmi destekler nitelikte idi. Yüksek plazma adrenokortikotropik hormondüzeyleri, artmış 24-saatlik idrar metanefrin ve normetanefrin düzeyleri ve ciddi hipokalemi olduğu görüldü. Abdomen bilgisayarlı tomografisinde sol adrenal bezde 3 cm boyutunda non-adenomatöz lezyon saptandı. Preoperatif hazırlık sonrası, sol adrenalektomi operasyonu yapıldı. Histopatolojik incelemede adrenokortikotropik hormon ile fokal boyanma gösteren 2,5 cm boyutunda feokromositoma rapor edildi. Operasyon sonrası hidrokortizon tedavisi ile taburcu edildi. Operasyondan altı hafta sonra, 24-saatlik idrar metanefrin ve normetanefrin düzeylerinin normal aralıkta olduğu görüldü. Sonuç olarak, adrenokortikotropik hormon-üreten feokromositoma ektopik Cushing sendromu düşünülen ve adrenal kitlesi olan hastalarda akılda bulundurulması gereken bir tanıdır.

Anahtar kelimeler: Ektopik Cushing sendromu; feokromositoma; ACTH boyama

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Introduction

Cushing's syndrome (CS) is characterized as inappropriately high levels of glucocorticoids; the signs and symptoms of disease result from the chronic exposure of tissues to glucocorticoids (1). Endogenous CS is an extremely rare disorder, wherein the majority of cases result from adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas. Ectopic ACTH production by a non-pituitary tumor such as bronchial carcinoid accounts for approximately 10-15% of CS cases (2). Remaining of the cases are ACTH-independent, and adrenal glands are responsible for excess steroids.

ACTH-producing pheochromocytoma is a rare cause of ectopic CS (3). In cases when pheochromocytomas co-secretes catecholamines and ACTH, they cause severe disease manifestations because of excess cortisol and catecholamine. The patients may present with classical signs and symptoms of CS. Adrenal mass, biochemical hallmarks of ACTH-dependent hypercortisolism, and elevated catecholamine levels indicate the presence of ACTH-secreting pheochromocytoma. We present a rare case of ectopic ACTH syndrome associated with pheochromocytoma.

Case Report

An informed consent was obtained from the patient for case report. A 55-year-old man who had undergone radiofrequency ablation for atrioventricular nodal reentrant tachycardia was consulted from cardiology to endocrinology because of resistant hypertension and hypokalemia. The patient suffered from severe proximal muscle weakness, fatigue, polyuria, and polydipsia. He had been diagnosed with type 2 diabetes mellitus and hypertension for three years. He had 30 pack-year smoking history.

During the physical examination, severe signs of CS were recorded such as proximal myopathy, central obesity with wasted extremities, easy bruising, skin atrophy, and plethora. No abdominal striae were detected. Blood pressure was recorded as 150/90 mmHg despite treatment with a combination of an angiotensinogen receptor blocker, a calcium antagonist, a thiazide diuretic, and a beta-blocker. Initial laboratory examination revealed severe hypokalemia (2.7 mmol/L [reference value: 3.5-5.1]). The tests were consistent with ACTH-dependent CS: abnormal low-dose dexamethasone suppression test (cortisol: 63.0 µg/dL; positive result: >1.8 µg/dL), elevated salivary cortisol (17.4 µg/dL, reference value: <0.43 µg/dL), elevated urinary cortisol (290 µg/24 h, reference value: 3.5-45 µg/24 h), loss of diurnal variation (morning cortisol: 57.8 µg/dL, late-night cortisol: 55.8 µg/dL), and high ACTH level: 241.0 (0-46.0) pg/mL. Thoraco-abdominal computerized tomography was performed for the etiological investigation of ectopic CS and revealed a 3.5-cm left adrenal mass with high precontrast Haunsfield unit value (31 HU) and low washout value (26%). T2-weighted magnetic resonance imaging showed a hyperintense mass on the left adrenal (Figure 1). A 24-hour urine collection study revealed elevated excretion of metanephrine (1187 µg/24 h, reference value: 0-374 µg/24 h) and normetanephrine (1078 µg/24 h, reference: 0-778 µg/24 h; Table 1).

For a possible malignancy that may also cause ectopic ACTH syndrome, metabolic imaging with fluorine-18 fluorodeoxyglucose ([18F]-FDG) positron emission tomography was performed. It revealed pathological FDG uptake in the adrenal mass and also on the right side of the lung. Because of tobacco use history, bronchoalveolar lavage and endoscopic bronchial biopsy were performed for excluding pulmonary malignancy. The results were compatible with pulmonary infection. He was treated with broad-spectrum antibiotics for potential infections. Left adrenalectomy was planned for the adrenal

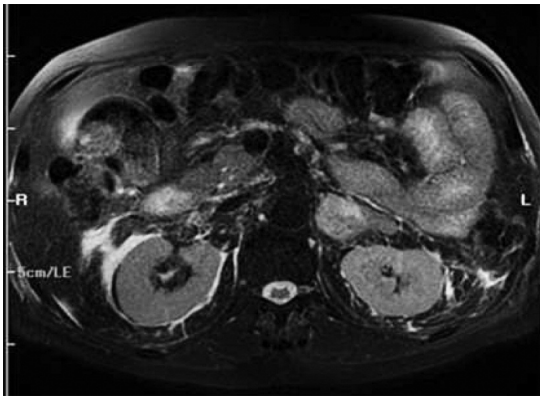

Figure 1: T2-weighted MRI shows high-signal pheochromocytoma in the left adrenal gland.

Table 1. Laboratory results before and after adrenalectomy.

Laboratory test	Preoperative	Six weeks after the operation	Reference range
Serum potassium (mmol/L)	2.7	4.5	3.5–5.1
HbA1c (%)	9.5	6.0	
Fasting plasma glucose (mg/dL)	211	85	70–100
24-hour urinary cortisol (mcg/24 h)	290	NA	3.5–45
Salivary cortisol (mcg/dL)	17.4	0.075	<0.43
Serum cortisol (mcg/dL)	57.8	10.9	6.2–19.4
Plasma ACTH (pg/mL)	241.0	43.1	0–46
Plasma aldosterone (ng/dL)	3.17	NA	0–16
PAC/PRA ratio (ng/dL to ng/mL/h)	5.7	NA	<20
24-hour urinary noradrenaline (mcg/24 h)	247.0	52.7	23–105
24-hour urinary adrenaline (mcg/24 h)	63.2	1.26	4–20
24-hour urinary metanephrine (mcg/24 h)	1187.0	11.2	0–374
24-hour urinary normetanephrine (mcg/24 h)	1078.0	328.0	0–778

NA: Non-available; ACTH: Adrenocorticotropic hormone; PAC: Plasma aldosterone concentration; PRA: Plasma renin activity; h: hour.

mass. Potassium replacement for hypokalemia and insulin for the treatment of diabetes were needed. Alpha-and then beta-blockers were used to control blood pressure and prevent an intraoperative hypertensive crisis. Furthermore, prophylactic anticoagulation was initiated.

Metyrapone treatment was initiated to control the symptoms of severe hypercortisolism. During metyrapone therapy, the patient suffered from dyspnea, fever, and hypoxia despite ongoing antibiotherapy and prophylactic anticoagulation. Bilateral infiltrates were seen on the chest radiograph. Trimethoprim-sulfamethoxazole and oxygenation with nasal cannula were initiated promptly because of the strong clinical suspicion of pneumocystis pneumonia (PCP). The clinical status improved with this treatment. Left adrenalectomy was performed without any complication. A histopathological examination revealed a 2.5-cm pheochromocytoma without necrosis, atypical mitoses, extra-adrenal extension, and vascular invasion. Additional immunohistochemical staining for ACTH was found to be focally positive (Figure 2). Perioperative corticosteroid coverage was administered and hydrocortisone replacement therapy was needed as maintenance therapy because of the long-standing suppression of hypothalamic-pituitary axis. Following surgery, hypokalemia, hypertension, and hyperglycemia resolved considerably. Insulin treatment was not required and antihypertensive medications were tapered. Furthermore, six weeks postoperatively, 24-hour urinary excretion of metanephrines and ACTH levels were within the normal range (Table 1).

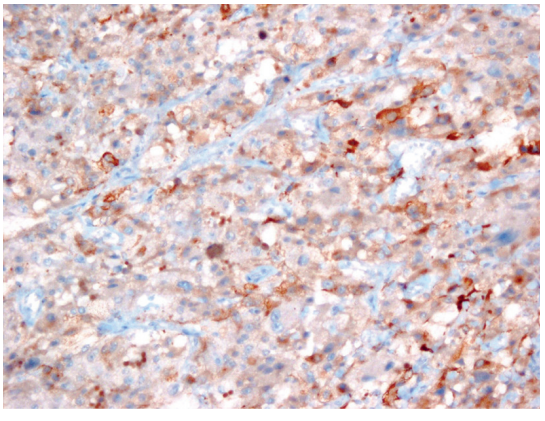

Figure 2: Histopathology of the adrenal mass: adrenomedullary tumor with immunopositive staining for ACTH (ACTH staining, IHC ×200).

Discussion

Pheochromocytoma is a rare cause of ectopic ACTH syndrome and presents a challenge to the clinician in the diagnosis and treatment. ACTH-secreting pheochromocytomas are the source of ACTH secretion in approximately 5% of ectopic ACTH-related CS. The cases were first described in 1964 by Bourgoignie et al. (4). Most of the cases included women and ranged in age from 26 to 74 years (5).

Our patient presented with resistant hypertension and hypokalemia. Hypertension is more common in ACTH-producing pheochromocytomas than other cases of ectopic CS (5, 6). It may be because of high cortisol levels coexisting with high catecholamine levels. High mineralocorticoid activity causes hypokalemia, as noted in our patient. High cortisol levels lead to mineralocorticoid activity because of saturating 11-β-hydroxysteroid dehydrogenase type 2 enzymes, which is responsible for cortisol metabolism.

In our case, the diagnosis of ACTH-producing pheochromocytoma was suspected because of hypercortisolism symptoms, high ACTH levels, and unilateral adrenal mass with high HU. High catecholamine levels supported the diagnosis. In 1979, Forman suggested the first criteria for the diagnosis of ACTH-secreting pheochromocytoma, which were revised by Chen in 1995 (7, 8). These criteria are (a) clinical and laboratory evidence of hypercortisolism, (b) high plasma ACTH levels, (c) biochemical evidence of pheochromocytoma and adrenal mass with a bright T2 signal in MRI, (d) resolution of signs and symptoms of excess cortisol and catecholamine after unilateral adrenalectomy, and (e) rapid normalization of plasma ACTH levels after adrenalectomy. Our patient met three criteria before surgery and the other two criteria were fulfilled after adrenalectomy.

Early diagnosis and preoperative preparation are important for complete remission without complications. Severe hypercortisolism may be a life-threatening condition, particularly in ectopic CS cases. Pulmonary thromboembolism, acute heart failure, acute respiratory failure, infections, and gut perforation should be considered. Prophylaxis and treatment with appropriate antibiotics for infections and anticoagulant prophylaxis for deep vein thrombosis should not be delayed. Steroidogenesis inhibitors may be used alone or in combination to control severe hypercortisolism, and patients with a serious disease may need intensive care unit management (9). Our patient was diagnosed with pneumonia during hospitalization, which required antibiotherapy and oxygenation. Metyrapone was initiated to control severe hypercortisolism and make the patient clinically stable before surgery. However, after the initiation of cortisol-lowering agents, PCP can be triggered because of immune reconstitution. PCP prophylaxis before the initiation of cortisol-lowering therapy is recommended (10).

Postoperatively, immunohistochemical markers indicated focally positive ACTH staining in our patient and supported the diagnosis. However, Cassarino et al. reported a case of suspected ACTH-producing pheochromocytoma with negative immunochemistry (11). This may be because of corticotropin-releasing hormone-producing pheochromocytomas. In addition, it has been hypothesized that high-molecular-weight ACTH that is not recognized by typical antibodies can be responsible for negative immunochemistry. Therefore, ACTH production of the tumor cannot be excluded by negative immunohistochemistry alone.

In conclusion, an ACTH-producing pheochromocytoma should be considered in patients with clinical manifestations of severe ectopic CS and adrenal mass. Early diagnosis and appropriate management of fatal complications, such as thrombosis and infections, are crucial for a successful surgery. In cases with severe hypercortisolism, preoperative preparation with steroidogenesis inhibitors should be considered.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Başak Bolayır, Müjde Aktürk, Nuri Çakır; Design: Alev Eroğlu Altınova,

Füsun Baloş Törüner; Control/Supervision: Füsun Baloş Törüner, Banu Aktaş Yılmaz; Data Collection and/or Processing: Başak Bolayır, Damla Okay, Aydın Tuncer Sel; Analysis and/or Interpretation: Aylar Poyraz, Murat Akın; Literature Review: Başak Bolayır, Damla Okay; Writing the Article: Başak Bolayır, Damla Okay; Critical Review: Alev Eroğlu Altınova, Füsun Baloş Törüner.

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