

# Ectopic ACTH Syndrome Caused by Multifocal Pulmonary Carcinoids with 18F-FDG Uptake: Case Report

## 18F-FDG Tutan Çok Odaklı Pulmoner Karsinoidlerden Kaynaklanan Ektopik ACTH Sendromu

İlkay ÇAKIR,<sup>a</sup>  
Tülay KAÇAR GÜVELİ,<sup>b</sup>  
Zeynep TAŞDEMİR,<sup>c</sup>  
Ramazan ALBAYRAK,<sup>d</sup>  
Kamil KAYNAK,<sup>e</sup>  
Şebnem BATUR,<sup>f</sup>  
Büge ÖZ,<sup>f</sup>  
Züleyha KARACA<sup>g</sup>

Clinics of

<sup>a</sup>Endocrinology,

<sup>b</sup>Nuclear Medicine,

<sup>c</sup>Chest Diseases,

<sup>d</sup>Radiology,

Bağcılar Training and Research Hospital,  
Departments of

<sup>e</sup>Thoracic Surgery,

<sup>f</sup>Pathology,

İstanbul University

Cerrahpaşa Faculty of Medicine,  
İstanbul

<sup>g</sup>Department of Endocrinology,

Erciyes University Faculty of Medicine,  
Kayseri

Geliş Tarihi/Received: 21.01.2016

Kabul Tarihi/Accepted: 22.03.2016

Yazışma Adresi/Correspondence:

İlkay ÇAKIR

Bağcılar Training and Research Hospital,  
Department of Endocrinology,

İstanbul,

TÜRKİYE/TURKEY

drilkcakir@hotmail.com

**ABSTRACT** Ectopic ACTH secretion [EAS] and bronchopulmonary carcinoids are both rare diseases, although lung carcinoids account for the most common source of EAS. Surgical resection of the tumor is selected treatment when the source of EAS could be determined. We report a patient with signs and symptoms suggestive of hypercortisolism, admitted to hospital with weight gain. Laboratory tests were in favour of ACTH-dependent Cushing's syndrome, a normal pituitary MRI and no central-to-peripheral ACTH gradient in bilateral inferior petrosal sinus sampling are suggested ectopic ACTH secretion. Thoracic CT scan revealed two lesions at the left lung, with 18F-FDG-uptake at PET scan. The patient was successfully treated with lobectomy and histological examination confirmed an atypical bronchial carcinoid tumor with positive ACTH immunoreactivity. Although functional imaging modalities that target somatostatin receptors in neuroendocrine tumours are favourable, FDG-PET imaging may also be a useful and more available tool for evaluation of thoracic carcinoid tumors.

**Key Words:** Cushing syndrome; carcinoid tumor; positron-emission tomography; fluorodeoxyglucose F18; ACTH syndrome, ectopic

**ÖZET** Bronkopulmoner karsinoid tümörler, ektopik ACTH salgımasının en sık nedeni olmakla birlikte, her ikisi de nadir görülen hastalıklardır. Ektopik ACTH salgımasının kaynağı belirlenebildiğinde seçilmiş tedavi tümörün cerrahi olarak çıkarılmasıdır. Hastaneye kilo artışı ile başvuran, hiperkortizolemi belirti ve bulguları saptanan bir olgu sunmaktayız. Laboratuvar bulguları ACTH-bağımlı Cushing lehine olan hastada hipofizer MR'ın normal olması ve bilateral inferior petrozal sinüs örneklemesinde santral-periferik ACTH gradientinin bulunmaması ektopik ACTH salgımasını düşündürdü. Toraks BT'de sol akciğerde iki adet lezyon saptandı, PET görüntülemesinde 18F-FDG tutulumu izlendi. Hasta başarılı bir lobektomi geçirdi ve histolojik inceleme ile ACTH immünreaktivitesi pozitif olan atipik bronşial karsinoid tanısı kondu. Her ne kadar nöroendokrin tümörlerde somatostatin reseptörlerini hedef alan fonksiyonel görüntülemeler revaçta ise de FDG-PET görüntüleme de torasik karsinoid tümörlerin değerlendirilmesinde yararlı ve daha kolay ulaşılabilir bir araç olabilir.

**Anahtar Kelimeler:** Cushing sendromu; karsinoid tümörü; pozitron emisyon tomografisi; fluorodeoksiglukoz F18; ACTH sendromu, ektopik

**Türkiye Klinikleri J Endocrin 2016;11(1):22-6**

The syndrome of "ectopic ACTH" secretion (EAS), which relates to sources other than the pituitary or adrenals, is a rare disease.<sup>1,2</sup> In course of remaining untreated, hypercortisolemia independent of its cause has significant morbidity and mortality. The lung diseases including small-cell carcinoma and bronchial carcinoid tumours usually constitute the most common causes of EAS.<sup>3</sup>

doi: 10.5336/endocrin.2016-50345

Copyright © 2016 by Türkiye Klinikleri

Diagnosis of ectopic ACTH syndrome contains difficulties due to lack of dynamic biochemical tests and imaging procedures with 100% accuracy.<sup>4</sup> Here, we present a 18-year old female with Cushing's Syndrome (CS) related to EAS from multifocal primary bronchopulmonary carcinoid tumors (BPCT), diagnosed by 18f-fluorodeoxyglucose (18f-FDG) PET/CT.

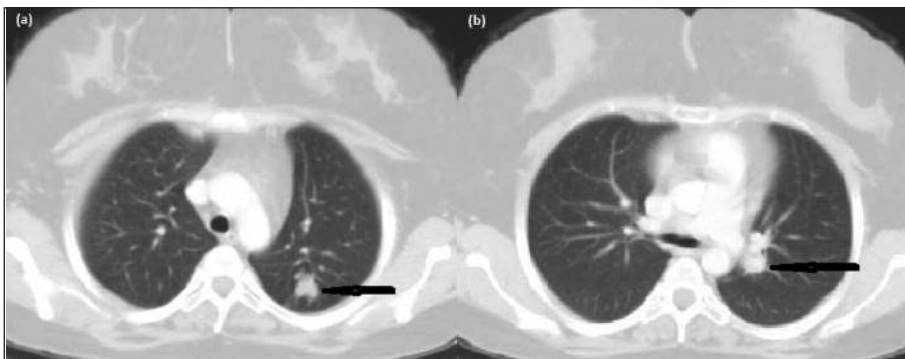
## CASE REPORT

A 18-year old girl was referred to endocrinology outpatient clinic with rapid weight gain. On physical examination, she demonstrated, plethoric moon face, buffalo hump, central obesity, multiple wide abdominal red striae and generalized muscle weakness. Her body mass index was 27 kg/m<sup>2</sup>. The remaining physical examination was normal, including blood pressure levels. She and her parents denied exogenous steroid usage.

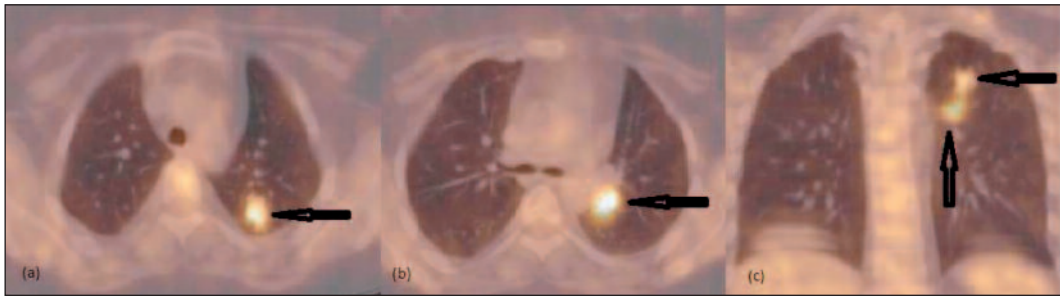
The overnight 1-mg dexamethasone screening test for CS yielded a non-suppressible plasma cortisol level of 30.79 µg/dL. She also failed the confirmatory low-dose dexamethasone suppression test with a cortisol level of 32.04 µg/dL after 2 days of dexamethasone loading. Loss of circadian rhythm of cortisol secretion was also consisted with CS. Plasma ACTH levels were measured twice and found elevated (117 pg/ml and 94 pg/ml respectively), serum potassium level was normal (4.11 mmol/l). Based to these clinical and laboratory findings, diagnosis of ACTH-dependent Cushing's syndrome was done. A high-dose dexamethasone test (8 mg) (HDDT) showed no

suppression of the cortisol or ACTH level. Pituitary magnetic resonance imaging (MRI) showed no direct or indirect signs of the presence of a pituitary adenoma. In addition, no central-to-peripheral ACTH gradient was observed in bilateral inferior petrosal sinus sampling (BIPSS). The computed tomography (CT) scan of the thorax revealed two lesions, both sized 16 mm in left lung, one in superior lobe apikoposterior segment, and the second in lingular lobe (Figure 1). At this point, although Gallium-68 Dototate PET-CT scan is the recommended imaging modality with demonstrated high sensitivity for identification of neuroendocrine tumours, which account for majority of the ectopic ACTH secreting tumours, we could perform PET-CT scan with 18f-FDG because of availableness in our medical center. The lesions showed uptake (early Standard Up-take Value (SUV)max 3.5, late SUVmax 6.3) (Figure 2). Based on these results, the patient underwent to lobectomy. The gross pathological examination demonstrated nodular solitary lesions measuring 2.2x2x1.5 cm. Microscopically the tumor cells were consisted of monotonous cells with hyperchromatic nuclei and acidophilic cytoplasm. There were focal necrotic areas, mitotic figures were recognized in 2 per 2 mm<sup>2</sup> (10 HPF). Lenfovacular invasion was present. Immunohistochemistry was positive for CD 56, ACTH, chromogranin and synaptophysin; Ki-67 score was 3% (Figure 3).

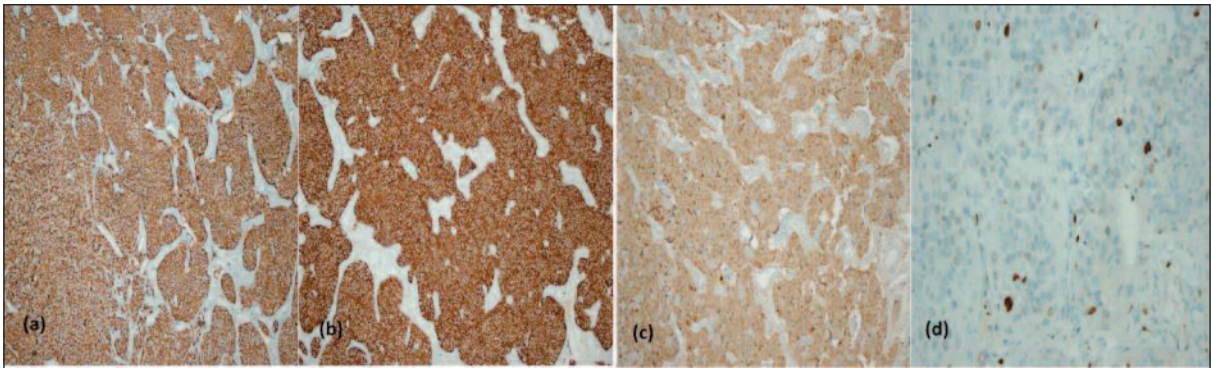
Postoperatively, her morning cortisol level was 0.296 µg/dL and ACTH level was 11.28 pg/ml with hypocortisolism symptoms so steroid replace-



**FIGURE 1:** Lesions sized 16 mm in left lung, in superior lobe apikoposterior segment (a); and in lingular lobe (b).



**FIGURE 2:** Axial images: Lesion -16 mm in diameter- fused FDG-PET/CT [from left to right] at apicoposterior space of left lung superior lobe [SUVmax:3.4] (a); Axial images: Second lesion-15-17 mm in diameter-fused FDG-PET/CT [from left to right] besides left lung bronchi [SUVmax:3.6] (b); Coronal images: Two separate lesions fused FDG-PET/CT [from left to right] at left lung superior lobe (c).



**FIGURE 3:** Tumour cells show immunoreactivity for CD56 (a) synaptophysin (b), ACTH (c) [Immunohistochemical staining, x100]; Proliferative index Ki67 [d] [Immunohistochemical staining, x400].

ment with prednisolone was started. She is doing well 2 months after operation and we are waiting for recovery of her own pituitary-adrenal axis.

## DISCUSSION

Endogenous Cushing's syndrome is an uncommon disorder affecting two to three persons per 1 million people.<sup>1</sup>

It may result from autonomous adrenal overproduction of cortisol or inappropriate excessive secretion of ACTH by pituitary corticotroph tumors (Cushing's disease) or ectopic ACTH production, usually from neuroendocrine tumors.<sup>2</sup> Here we report a patient with an ectopic ACTH-secreting primary lung carcinoid tumor who presented with cushingoid appearance. Bronchopulmonary carcinoid tumors represent 1% to 5% of all primary lung tumors, however the incidence of BPCT as cause of Cushing's syndrome remains variable in the literature, ranging from 1%

to 10%, but these tumours are reported to be the most common source of ectopic ACTH secretion, at 25-35%.<sup>5-7</sup>

The majority of patients, with BPCTs, present insidiously with the symptoms, cough, hemoptysis, and pneumonia (classical triad), but a functional presentation with symptoms related to hormonal secretion is rare (1-3%).<sup>5</sup> Our patient didn't report any chest symptoms, her cushingoid appearance led the definition of the tumours. The most common laboratory findings of ectopic ACTH syndrome; hypokalemia, hypokalemic alkalosis and extremely high circulating ACTH concentrations were absent also in accordance with a series of 10 ECS, authors report a low hypokalemia incidence as 10%.<sup>8,9</sup> Although the average age at diagnosis of typical lung carcinoids is 45 years-the same for both sexes-whereas patients with atypical carcinoids are usually determined 10 years older and notably more often develop lymph node metastases, this 18-year

old young girl could be diagnosed relatively earlier through the consequences of ectopic ACTH secretion. Most of the atypical carcinoid tumors arise sporadically in contrast to other lung tumors including large-cell- neuroendocrine tumors and small-cell lung cancers which are related with smoking.<sup>10</sup>

Our patient is also non-smoker and to our knowledge one of the youngest patients in the literature.

Recognizing Cushing's syndrome is usually easier than determining the source when ACTH oversecretion is subject. There isn't a dynamic biochemical tests achieves 100% accuracy. Typically, in EAS, the degree of ACTH hypersecretion and excretion of urinary free cortisol is much higher than compared to Cushing's disease. CRH stimulation usually results in increase in ACTH and cortisol levels in Cushing's disease, but not in EAS. The HDDT when combined with CRH stimulation test usually differentiates EAS from Cushing's disease reasonably well however as mentioned in previous reports nearly 25% of patients with EAS have false-positive responses to dexamethasone and/or CRH stimulation tests.<sup>4</sup> BIPSS is considered the gold standard for differential diagnosis with a sensitivity of 88-100% and a specificity of 90-100%. Rarely, false negatives also can occur with BIPSS and are related to incorrect catheter placement or anomalous venous drainage or anatomy.<sup>4</sup> In our case, dynamic biochemical tests and BIPSS were in favour of EAS.

Localization of these tumors is challenging, and the optimal imaging approach is not established yet. It is recommended to start by imaging the chest, as most ACTH secreting tumours are located there. CT and MRI are anatomical scans that locate most tumours; however, functional studies scans may be necessary when faced with no, double or more tumours. Octreotide or pentetretotide scintigraphy or Gallium-68 Dototate PET-CT scan use tracers to target somatostatin receptors, (SSR types 2 and 5) which are expressed on the cell-surface of most neuroendocrine tumours. Therefore, play a major role in detecting these tumours. Some papers report limited value of 18-FDG PET CT in detecting neuroendocrine tumours, due to low proliferative activity of these tumours.<sup>11,12</sup> However this examination was positive in our case, in accordance with the findings of Daniels et al who demonstrated a trend toward higher PET sensitivity for atypical carcinoid tumors in their cohort.<sup>13</sup>

A multidisciplinary approach is required in order to diagnose and localise ACTH oversecretion. Although number of therapeutic options and diagnostic procedures are increasing, a personalized approach may be cost and time effective. The reported young patient with two atypical lung carcinoid tumors secreting ACTH exhibits a demonstrative profile for this position. Due to rarity of syndrome, reported case series or shared one center experiences are limited, individual case reports may be helpful in understanding and solving pitfalls in the full spectrum of disease.

## REFERENCES

1. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The Diagnosis of Cushing's Syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008;93(5):1526-40.
2. Raff H, Sharma ST, Nieman LK. Physiological basis for the etiology, diagnosis, and treatment of adrenal disorders: Cushing's syndrome, adrenal insufficiency, and congenital adrenal hyperplasia. *Compr Physiol* 2014;4(2):739-69.
3. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet* 2006;367(9522):1605-17.
4. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *J Clin Endocrinol Metab* 2005;90(8):4955-62.
5. Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM. Bronchopulmonary neuroendocrine tumors. *Cancer* 2008;113(1):5-21.
6. Scanagatta P, Montresor E, Pergher S, Mainente M, Bonadiman C, Benato C, et al. Cushing's syndrome induced by bronchopulmonary carcinoid tumours: a review of 98 cases and our experience of two cases. *Chir Ital* 2004;56(1):63-70.
7. Alexandraki KI, Grossman AB. The ectopic ACTH syndrome. *Rev Endocr Metab Disord* 2010;11(2):117-26.
8. Torpy DJ, Mullen N, Ilias I, Nieman LK. Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: a series of 58 cases. *Ann N Y Acad Sci* 2002;970:134-44.

9. Tsirona S, Tzanela M, Botoula E, Belenis I, Rondogianni D, Tsagarakis S. Clinical presentation and long-term outcome of patients with ectopic ACTH syndrome due to bronchial carcinoid tumors: a one-center experience. *Endocr Pract* 2015;21(10):1104-10.
10. Kaifi JT, Kayser G, Ruf J, Passlick B. The diagnosis and treatment of bronchopulmonary carcinoid. *Dtsch Arztebl Int* 2015;112(27-28):479-85.
11. Venkitaraman B, Karunanithi S, Kumar A, Bal C, Ammini AC, Kumar R. 68Ga-DOTATOC PET-CT in the localization of source of ectopic ACTH in patients with ectopic ACTH-dependent Cushing's syndrome. *Clinical Imaging* 2014;38(2):208-11.
12. Kayani I, Conry BG, Groves AM, Win T, Dickson J, Caplin M, et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. *J Nucl Med* 2009;50(12):1927-32.
13. Daniels CE, Lowe VJ, Aubry MC, Allen MS, Jett JR. The utility of fluorodeoxyglucose positron emission tomography in the evaluation of carcinoid tumors presenting as pulmonary nodules. *Chest* 2007;131(1):255-60.