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Overlapping Between Thymus Neuroendocrine Carcinoma as an Ectopic Cushing Syndrome and Exogenous Cushing's Syndrome: A Case Report

Ektopik Cushing Sendromu Olan Timus Nöroendokrin Karsinomu ile Ekzojen Cushing Sendromu Örtüşmesi: Bir Olgu Sunumu

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Abstract

Cushing's syndrome results from an excess production of the hormone cortisol by the adrenal gland. It can be distinguished into ectopic and exogenous, also known as iatrogenic, depending on whether the cause exists inside or outside the body, respectively. The exogenous disease can occur due to the intake of corticosteroids medication. Thymic neuroendocrine carcinoma is one of the most common etiologies of ectopic Cushing's syndrome. We report a case of overlapping condition between ectopic and exogenous Cushing's syndromes and discussed the invasive characteristics of thymic low-grade neuroendocrine carcinoma and its capability to transform to a high-grade carcinoma. A 29-year-old male patient was presented with Cushing's symptoms and hypokalemia. He had a history of repeated weekly dexamethasone injections during last year to treat generalized weakness, without physician's prescription. He reported relative improvement in his general condition with the use of corticosteroids. The case was managed as an iatrogenic Cushing's syndrome because of excessive use of corticosteroids and low cortisol levels despite suppressed ACTH. He presented with weakness and hypercortisolism eight months after the discontinuation of dexamethasone with an ACTH >1.500 pg/mL; these features were in favor of ectopic Cushing's syndrome. Also, a thymus mass was detected on imaging. We performed thymus resection due to the early stage of the syndrome and there was no sign of metastasis to other organs. Pathology reported a thymic carcinoid tumor. Normal calcium, PTH, prolactin, and gastrin levels ruled out the involvement of MEN I. Tumor cells were immunoreactive for ACTH, and a whole body scan was performed. An 18-month delay in visiting the doctor and not undergoing whole body scan led to a severe relapse with full-blown Cushing's syndrome, generalized bone pain, pulmonary metastatic nodules, hyperplasic adrenals, and widespread bone metastases as demonstrated by the whole body bone scan. Bilateral adrenalectomy was performed. Metastatic neuroendocrine carcinoma grade III was reported in the pathology. After consultation with an oncologist, palliative chemotherapy with octreotide was started. He died because of pulmonary metastases, severe opportunistic organism infections, and septic shock. This case represented one of endogenous hypercortisolism (ectopic Cushing's syndrome) masked by the excess exogenous use of glucocorticoids, with unexpected relapse of localized and lowstage thymus neuroendocrine carcinoid tumor. Its conversion to invasive type within less than two years after thymus resection led to adrenals, lungs, and all bones metastases.

Keywords: Bilateral adrenal hyperplasia; ectopic Cushing's syndrome; exogenous Cushing's syndrome; octreotide; thymus neuroendocrine carcinoma

Özet

Cushing sendromu, adrenal bez tarafından kortizol hormonunun fazla üretimi sonucu gelişmektedir. Buna yol açan sebebin vücudun içinde veya dışında oluşuna göre ektopik ve ekzojen -iyatrojenik olarak da bilinir- şeklinde ayırt edilebilmektedir. Ekzojen hastalık, kortikosteroid ilaç alımına bağlı olarak ortaya çıkabilmektedir. Timik nöroendokrin karsinom, ektopik Cushing sendromunun en sık görülen etiyolojilerinden biridir. Bu çalışmada, ektopik ve ekzojen Cushing sendromlarının örtüştüğü bir vaka sunulmuş ve timik düşük dereceli nöroendokrin karsinomun invaziv özelliklerinin ve yüksek dereceli bir karsinoma dönüşme yeteneğinin tartışılması amaçlamıştır. Yirmi dokuz yaşındaki erkek hasta, Cushing semptomları ve hipokalemi ile başvurdu. Doktor reçetesi olmaksızın, genel halsizliği tedavi etmek için son bir yıl boyunca tekrarlanan haftalık deksametazon enjeksiyonu öyküsü vardı. Hasta, genel kondisyonunda kortikosteroid kullanımı ile rölatif bir düzelme olduğunu bildirdi. Süprese ACTH'ye rağmen düşük kortizol düzeyleri ve aşırı kortikosteroid kullanımı nedeniyle olgu, iyatrojenik Cushing sendromu olarak ele alındı. Deksametazonun kesilmesinden sekiz ay sonra ACTH düzeyi >1,500 pg/mL olan hasta, hiperkortizolizm ve hâlsizlik ile başvurdu; bu özellikler ektopik Cushing sendromu lehine idi. Ayrıca, görüntülemede timus kitlesi saptandı. Sendromun erken evrede olması nedeniyle timus rezeksiyonu yapıldı ve diğer organlara metastaz belirtisi görülmedi. Patoloji tarafından timik karsinoid tümör rapor edildi. Normal kalsiyum, PTH, prolaktin ve gastrin düzeyleri ile MEN I dışlandı. Tümör hücreleri ACTH için immünreaktif idi ve tüm vücut taraması yapıldı. Doktor kontrolüne 18 aylık bir gecikme ile gelinmesi ve tam vücut taraması yapılmaması; tam teşekküllü Cushing sendromu, yaygın kemik ağrısı, pulmoner metastatik nodüller, hiperplazik adrenaller ve tam vücut kemik taramasında gösterildiği gibi yaygın kemik metastazları olan ciddi bir nükse neden oldu. Bilateral adrenalektomi yapıldı. Patoloji tarafından metastatik nöroendokrin karsinom grade III olarak rapor edildi. Bir onkologla istişarede bulunulduktan sonra, oktreotid ile palyatif kemoterapiye başlandı. Hasta pulmoner metastazlar, ciddi fırsatçı organizma enfeksiyonları ve septik şok nedeni ile kaybedildi. Bu hastada, aşırı ekzojen glukokortikoid kullanımıyla maskelenmiş endojen hiperkortizolizm (ektopik Cushing sendromu) ile lokalize ve düşük evre timus nöroendokrin karsinoid tümörün beklenmedik şekilde nüksü ve timus rezeksiyonundan sonra iki yıldan kısa bir süre içinde invaziv tipe dönüşerek adrenalde, akciğerde ve tüm kemiklerde metastazlara yol açması sunulmuştur.

Anahtar kelimeler: Bilateral adrenal hiperplazi; ektopik Cushing sendromu; ekzojen Cushing sendromu; oktreotid; timus nöroendokrin karsinomu

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Introduction

Ectopic Cushing's syndrome constitutes one-fifth of all adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome causes and one-tenth of all Cushing's syndrome etiologies. The most common etiology of ectopic Cushing's syndrome is the formation of bronchial carcinoids (1). Thymic carcinoid tumor also has a relatively high prevalence ectopic Cushing's syndrome causes with a progressive pattern (2). The presentation of carcinoid and neuroendocrine carcinoma of the thymus, as an ectopic ACTH-induced Cushing's syndrome, is very rare (3). Neuroendocrine carcinoid is characterized by multiple neurosecretory granules that release ACTH or rarely CRH leading to Cushing's symptoms (4, 5). Clinical presentations along with imaging and hormonal laboratory data assist in specifying the primary site of ectopic secretion of ACTH (1). The aim of this case presentation is to report the masking effect of ectopic Cushing's syndrome by an excess exogenous use of corticosteroids. Despite being pathologically low grade, it can progress invasively within months even after complete resection of the thymus.

Case Report

A 29-year-old male patient, without any previous medical problem, reported to the clinic with swelling of legs and weight gain of 35 kg during 1 year. The patient stated self-prescribed multiple dexamethasone injections weekly during last year to counter generalized weakness and reported relative improvement in his general condition by the use of the corticosteroid. On physical examination, obvious purple striates at the lower part of abdomen with at least 2 cm transverse diameter, non-pitting lower extremity edema, truncal obesity, moon face appearance, and some degree of proximal myopathy were observed. Blood pressure was measured to be 138/94 mmHg. On initial assessment, hypokalemia (K: 2.9 mEq/L), normal range of aldosterone (88 pg /mL), low cortisol (8:00 a.m.) level (2 µg/dL), low level of 24-h-urine free cortisol excretion (3.6 µg/24 h), and suppressed ACTH (6 pg/mL) were reported. With low cortisol and suppressed ACTH along with a history of excessive exogenous corticosteroids injection, iatrogenic Cushing's syndrome was suggested as the most probable diagnosis. The patient was discharged with glucocorticoid tapering and discontinuation. Despite recommendations for followup visits, he did not have any medical visit during eight months after discharge. Aftereight months, he reported to the clinic with lower extremity swelling and hypertension with blood pressure (BP) of 147/98. He denied any corticosteroid injection after discharge. On re-evaluation, high cortisol $_{8A.M.}$ (122 µg /dL), high 24-h-urine free cortisol excretion (221 µg/24 h), positive low-dose dexamethasone test (plasma cortisol, 87 µg/dL after 0.5 mg dexamethasone q6h for two days) with very high ACTH (>1500 pg /mL) were reported. Because of the likely involvement of the most probable ACTH-dependent Cushing's syndrome, we conducted tests for the analysis of primary site of ACTH secretion. The chest X-ray (CXR) demonstrated wide mediastinum and obtuse angle carina. Thoracic computed tomography (CT) scan without contrast showed anterior mediastinal mass with a size of 66 × 47 mm and some calcified foci. Based on the imaging findings, thymoma was the most likely diagnosis. Abdominal and pelvic CT-scan showed no evidence of other organ involvement. Thymectomy was performed at the same admission. During surgery, a completely encapsulated mass was seen. Thymic carcinoid tumor (typical type) without capsular invasion was reported in mediastinal mass pathology. There was no involvement of lymph nodes. Immunohistochemistry (IHC) showed positive epithelial membrane antigen (EMA), neuron-specific enolase (NSE), and chromogranin. A staining and negative carcinoembryonic antigen (CEA), SD45, and CD117 staining. Further, tumor cells were immunoreactive for ACTH. Normal serum calcium, parathyroid hormone (PTH), prolactin, and gastrin levels ruled out probable MEN I. Chromogranin A level after surgery was 34.1 ng/mL (normal range <36.4 ng /mL). We considered the case to be an early stage of thymic carcinoid tumor (stage I), and therefore, in addition to thymectomy, no further chemotherapy or radiotherapy was performed. Whole body scan was requested to detect the possible hidden metastases. In the first month after

thymectomy, normal ACTH and cortisol levels were obtained. The patient did not undergo a whole body scan despite our emphasis and did not visit the clinic for follow-up. After 18 months, he presented with lower extremity swelling, obesity, and generalized body bone pain with high alkaline phosphate (ALP) of 1,414 IU/L. As suspected, a whole body scan showed widespread multiple bone metastases (Figure 1). The chest-CT-scan, without contrast, reported right paratracheal, subcarinal, and bilateral pulmonary hilum lymphadenopathy, 8-mm pulmonary nodules, and bilateral pleural effusion in the presence of bilateral adrenal hyperplasia. Bilateral adrenalectomy was performed. The pathology report mentioned neuroendocrine type carcinoma grade III. The IHC showed positive CK, NSE, chromogranin, and Ki67 staining and negative TTF1 and CD45 staining. He was discharged with prednisolone 10 mg daily and fludrocortisone 0.1 mg daily and was referred to an oncologist who started palliative chemotherapy with octreotide. After two months, he was admitted to the hospital with fever, dyspnea, and respiratory distress. Multiple mixed lytic and blastic bone lesions in all spinal bones and ribs and scapula were seen. The mosaic pattern in lung parenchyma, patchy alveolar consolidations, and multiple pulmonary nodules were observed in the chest CTscan (Figure 2). He was admitted to intensive care unit (ICU) with respiratory distress and was intubated. With high suspicion to opportunistic organism-induced pneumonia, bronchoscopy and pleurocentesis were done. The pleural culture showed the presence of *Pneumocystis carinii*. Meropenem, ciprofloxacin and cotrimoxazole were started. Unfortunately, he died of severe sepsis and multiple pulmonary metastases in the ICU.

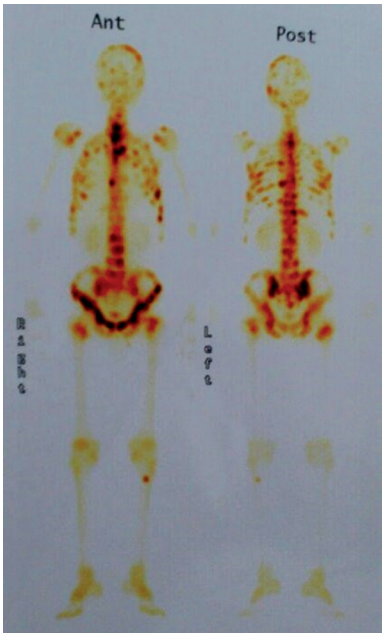

Figure 1: Widespread bone metastases in whole body scan 18 months after the thymic neuroendocrine carcinoma resection that is indicative of its invasive hematogenous spread.

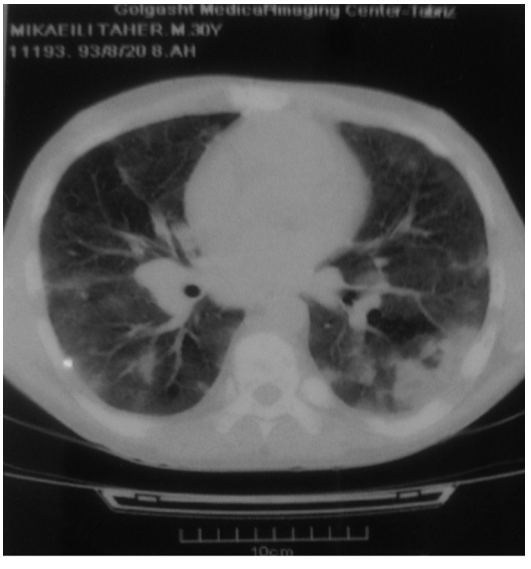

Figure 2: Patchy alveolar consolidations because of opportunistic organism induced pneumonia and metastatic pulmonary nodules in both lungs with the origin of thymic neuroendocrine carcinoma after bilateral adrenalectomy.

Discussion

Carcinoid tumors are characterized by the expression of somatostatin receptors. Positron emission tomography (PET)/CT, based on isotope labeling, should assist in the diagnosis of neuroendocrine tumors in earlier stages (6, 7). Aktas et al. suggested the use of 18F-FDG PET/CT scan to detect the ectopic site of ACTH-secreting tumors when ectopic Cushing's syndrome is the most probable diagnosis. In our case, 18F-FDG PET/CT scan showed diffused and increased uptake in bilateral adrenal hyperplasia with low FDG affinity in neuroendocrine mass indicating the tumor to be

of low grade (8). According to Matejka et al., somatostatin receptor scintigraphy, using 111Indium–octreotide and 99mTechnetium-albumin macroaggregates, can detect undetectable ACTH-secreting neuroendocrine carcinoid tumors (9). Andrés et al. reported a 50-year-old male patient with thymic carcinoid, which unlike the usual course, led to ectopic Cushing's syndrome without any metastases. The patient received multimodal treatment and showed complete clinical and biochemical response (2). Schalin-Jäntti et al. reported a 41-year-old male patient with well-differentiated thymic neuroendocrine carcinoma after resection that was detected with CT-scan. It was in remission for six years. After relapse, fluorine-labeled dihydroxyphenylalanine ((18) F-DOPA) PET/CT detected an uptake of the isotope at mediastinum that was resected (10). About 95% of thymic neuroendocrine tumors have metachronous metastasis and therefore should be followed-up (11). Nodal metastasis is common in thymic neuroendocrine tumors and serves as an important prognostic factor in the surveillance of these tumors (12). Initially, this patient presented with ectopic Cushing's syndrome masked by exogenous Cushing's syndrome and ACTH level. After eight months, a discontinuation of exogenous corticosteroid userevealed his hidden ectopic Cushing's syndrome. Thymus mass was detected on medical investigations. After clearly distinguishing ectopic Cushing's syndrome and thymus mass, we decided to perform a resection of thymus carcinoid owing to an early stage (stage I) and involvement of no other organ. In this case, despite the early stage of thymus carcinoid tumor, we incredibly faced thymus carcinoid relapse with adrenal metastases, pulmonary and bone metastases after 18 months, and high-grade differentiation of tumor to grade III neuroendocrine carcinoma. The invasive character and poor prognosis, even after complete resection of carcinoma, led to its spread via the hematogenous path, and unfortunately, the patient died from opportunistic organism-induced severe sepsis and multi-organ metastases. This case presents an example of masking ectopic Cushing's syndrome by exogenous Cushing's syndrome. The masking feature, owing to its aggressive pattern, in turn, converts the low-grade thymic neuroendocrine carcinoma to an invasive type within a period of less than two years. Thus, frequent follow-ups are essential to detect any relapse.

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Conflict of Interest

No conflict of interest was declared by the authors.

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Author Contributions

Concept: Esmail Faraji; Design: Esmail Faraji; Data Collection or Processing: Sepideh Tahsini Tekantapeh; Analysis or Interpretation: Sepideh Tahsini Tekantapeh; Literature Search: Esmail Faraji; Writing: Sepideh Tahsini Tekantapeh.

References

1. Alexandraki KI, Grossman AB. The ectopic ACTH syndrome. Rev Endocr Metab Disord. 2010;11:117-126. [Crossref] [PubMed]
2. Andrés R, Mayordomo JI, Ramón y Cajal S, Tres A. Paraneoplastic Cushing's syndrome associated to locally advanced thymic carcinoid tumor. Tumori. 2002;88:65-67. [PubMed]
3. Arora R, Gupta R, Sharma A, Dinda AK. Primary neuroendocrine carcinoma of thymus: a rare cause of Cushing's syndrome. Indian J Pathol Microbiol. 2010;53:148-151. [Crossref] [PubMed]
4. Carrillo-Muñoz A, Onofre-Borja M, Borrego-Borrego R, Chávez-Mercado L, Navarro-Reynoso FP, Ibarra-Pérez C. Atypical intermediate-grade mediastinal carcinoid. Case presentation. Cir Cir. 2011;79:191-195.
5. Dutta D, Mukhopadhyay S, Maisnam I, Ghosh S, Mukhopadhyay P, Chowdhury S. Neuroendocrine carcinoma of the thyroid causing adrenocorticotrophic hormone-dependent Cushing's syndrome. Thyroid. 2013;23:120-123. [Crossref] [PubMed]
6. Asha HS, Sudeep K, Alexander M, Korula A, Gnanamuthu BR, Thomas N. Cushing's syndrome in a case of thymic carcinoma. Indian J Endocrinol Metab. 2011;15:346-348. [Crossref] [PubMed] [PMC]

7. de Perrot M, Spiliopoulos A, Fischer S, Totsch M, Keshavjee S. Neuroendocrine carcinoma (carcinoid) of the thymus associated with Cushing's syndrome. Ann Thorac Surg. 2002;73:675-681. [Crossref]
8. Aktas GE, Soyluoglu Demir S, Sarikaya A. Bilateral symmetrical adrenal hypermetabolism on FDG PET/CT due to Cushing syndrome in well differentiated neuroendocrine carcinoma. Rev Esp Med Nucl Imagen Mol. 2015;35:118-120. [Crossref] [PubMed]
9. Matejka G, Toubeau M, Bernard A, Belleville Y, Vaillant G, Brun JM. [Thymic carcinoid tumor causing paraneoplastic Cushing syndrome. Diagnostic value of double-labelled tomoscintigraphy]. Presse Med. 1996;25:1201-1202. [PubMed]
10. Schalin-Jäntti C, Asa SL, Arola J, Sane T. Recurrent acute-onset Cushing's syndrome 6 years after removal of a thymic neuroendocrine carcinoma: from ectopic ACTH to CRH. Endocr Pathol. 2013;24:25-29. [Crossref] [PubMed]
11. Christakis I, Qiu W, Silva Figueroa AM, Hyde S, Cote GJ, Busaidy NL, Williams M, Grubbs E, Lee JE, Perrier ND. Clinical features, treatments, and outcomes of patients with thymic carcinoids and multiple endocrine neoplasia type 1 syndrome at MD Anderson cancer center. Horm Cancer. 2016;7:279-287. [Crossref] [PubMed]
12. Weksler B, Holden A, Sullivan JL. Impact of positive nodal metastases in patients with thymic carcinoma and thymic neuroendocrine tumors. J Thorac Oncol. 2015;10:1642-1647. [Crossref] [PubMed]