CASE REPORTS

THE TYPICAL CARCINOID TUMOR CASES CAUSINGECTOPIC ACTH SYNDROME: DRAMATIC RESPONSE TO SURGERY

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Abstract

Introduction: *Although Cushing's Syndrome (CS) is usually caused by pituitary/adrenal adenomas, in the remaining few cases, Adrenocorticotrophic hormone (ACTH) is secreted by extrapituitary neuroendocrine tumors (NET). In typical pulmonary / bronchial carcinoid tumors leading to ectopic ACTH syndrome (EAS). The main principle of treatment is the localization of the ACTH-secreting tumor and its surgical removal. In this case report, we aimed to present two typical carcinoid cases, whose ACTH and cortisol levels returned to normal after lung surgery for ectopic ACTH. One of the cases, a 32-year-old female patient with CS symptoms and signs, was referred to our department after detecting a lesion in the left lower lobe in the thorax CT, which did not show an obvious focus on cranial MRI. The other patient, a 36-year-old male, had previously undergone adrenalectomy for Cushing's syndrome and was admitted to the emergency department due to adrenal insufficiency. The lesion seen in the right lower lobe on thorax CT was evaluated as an ectopic ACTH focus. After the tumors of the patients were resected according to surgical principles, CS clinic regressed, and ACTH and cortisol values returned to normal. Pathological examinations of the surgically resected tumors were reported as typical carcinoid. With surgically removed typical carcinoids tumors, excellent long-term survival results can be achieved and hypercortisolism can be controlled.*

Keywords: *carcinoid tumor, surgical resection, ectopic ACTH syndrome, ectopic Cushing syndrome.*

INTRODUCTION

Cushing's Syndrome (CS) is usually caused by pituitary or adrenal adenomas. CS cases caused by pituitary tumors constitute 90% of all cases. In the very few remaining cases, Adrenocorticotropic hormone (ACTH) is secreted by extrapituitary neuroendocrine tumors (NETs) and may cause Ectopic Cushing's Syndrome (ECS) [1]. ECS is usually caused by ectopic ACTH syndrome (EAS) and constitutes 20% of ACTH-dependent CS and 10% of all CS [2]. EAS is usually caused by tumors located in the thoracic cavity and 50% of these tumors are of bronchopulmonary origin and 30% are mediastinal tumors [1]. Small Cell Lung Cancer (SCLC), pulmonary-bronchial carcinoid tumors and medullar carcinoma of the thyroid gland are the most common EAS-associated tumors [3]. The diagnosis of CS is primarily made with elevated morning fasting glucose, serum cortisol, 24-hour urine cortisol, and midnight plasma cortisol levels. In typical pulmonary/bronchial carcinoid tumors that cause ECS, the main principle of treatment is the localization of the ACTH secreting tumor and its surgical removal. We aimed to present a case of typical carcinoid tumor causing ECS and successfully treated with surgery.

CASE PRESENTATION

Case 1

32-year-old female patient with CS symptoms and signs admitted to the endocrinology department. Cranial MRI was normal and thoraco-abdominal CT was performed for detecting foci of ECS. A nodule with 22 x 15 mm dimeter was detected in the left lower lobe of lung in thorax CT (Figure 1a). There was pathologic increase uptake of 18f-DG on nodule on PET-CT (SUVmax:11.78, Figure 1b). 24-hour urinary cortisol value was reported as >1828 mcg/24h. Since no ACTH gradient difference was detected in IPSS, the patient was diagnosed as EAS. The patient underwent left lower lobectomy and mediastinal lymph node dissec-

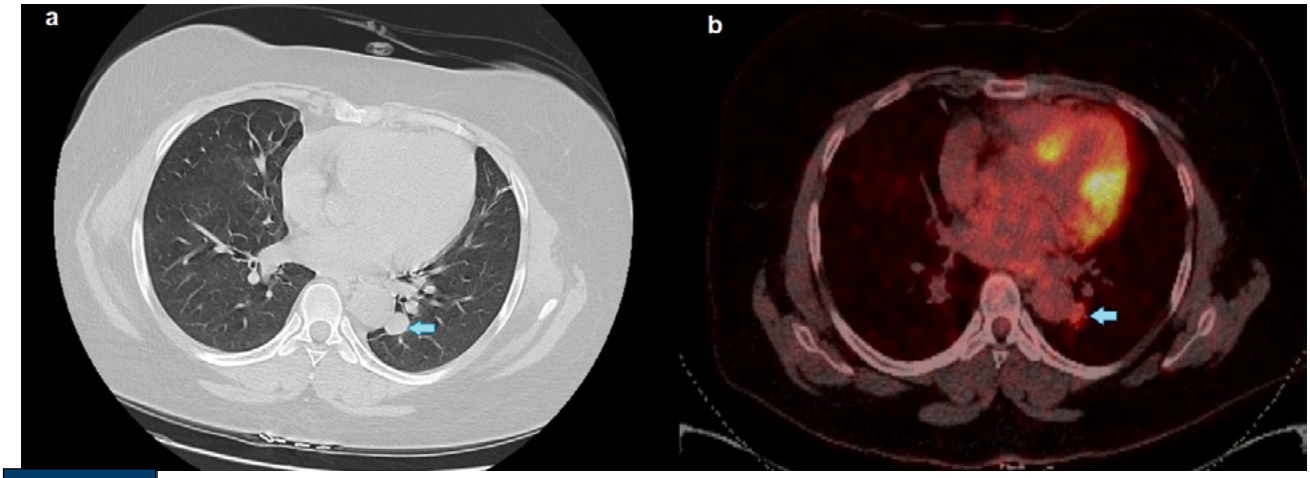

Figure 1

1a. Thorax CT shows, a pulmonary lesion with 22x15 mm diameter in left lower lobe.
1b. PET-CT shows that there is a pathological increase uptake of 18f-FDG on pulmonary nodule.

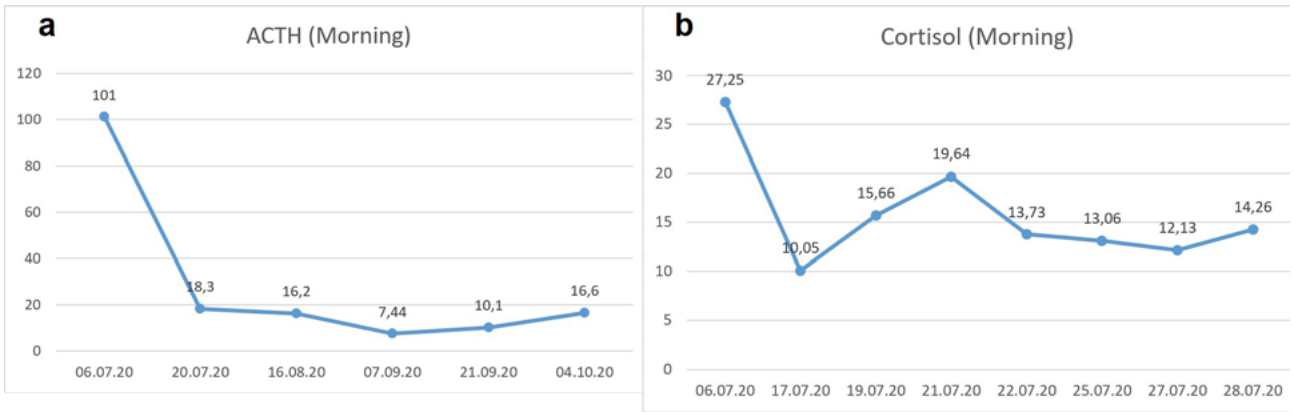

Figure 2

2a. A graphical representation of pre and postoperative serum ACTH levels.
2b. The graphic shows decreasing of morning serum cortisol levels dramatically in postoperative period.

tion via VATS after the frozen examination of the lesion was reported as a neuroendocrine tumor. The final histopathological examination was reported as a typical carcinoid tumor (pT1N0). In post-operative follow-up, serum cortisol level was determined to be 13.3 mcg/dL and 24-hour urinary cortisol level decreased (Figure 2a-b). The patient was discharged when she no longer needed antihypertensive and potassium replacement.

Case 2

A 36-year-old male patient referred to the endocrinology department with CS symptoms. The patient's plasma ACTH value resulted as 296 pg/mL. ACTH focus could not be detected in the pituitary MRI and whole-body tomography scan. Thorax CT performed to detect ectopic CS focus showed a nodule with 15 x 10 mm diameter in the right lower lobe (Figure 3). Right lower lobectomy and mediastinal lymph node dissection was performed after the frozen examination of the lesion was reported as a neuroendocrine tumor. In histopathological examination, the lesion was reported as a typical carcinoid tumor. The patient was discharged after his CS symptoms regressed and his morning ACTH and cortisol levels returned to normal. CS symptoms and signs were not observed in the follow-ups of both patients who were considered to be in complete remission.

DISCUSSION

In this case report, we aimed to present a carcinoid tumor that caused ECS and was both diagnosed and treated surgically. The correlation between cancer and CS was first demonstrated in 1928. Meador et al. showed ACTH activity in pulmonary carcinoids in 1962[4]. Among paraneoplastic syndromes in carcinoid tumors, ECS is the second most common paraneoplastic syndrome after carcinoid syndrome [5]. 1-2% of pulmonary NETs have been

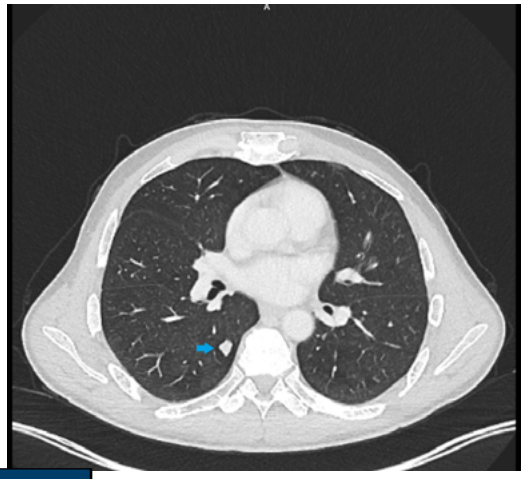

Figure 3 *A solitary pulmonary nodule that suspected ectopic focus for Cushing syndrome is seen at the right lower lobe on thorax CT.*

associated with CS. The diagnosis is made by the clinical characteristics of CD and the underlying malignancy, serum and 24-hour urine cortisol levels, and high ACTH levels. In EAS patients, cortisol is not suppressed with high-dose (8mg) DST and the pituitary gland responds negatively to corticotropin releasing hormone (CRH). However, ACTH suppression can be seen in some patients with high dose DST. For this reason, IPSS, which is the gold standard test, should be performed. The presence of CS characteristics and increased serum cortisol, 24-hour urinary cortisol and ACTH levels made the diagnosis of CS in our patients. With high-dose (8 mg) DST no suppression was observed. The absence of ACTH gradient difference between periphery and sinus in IPSS supported the diagnosis of EAS.

Despite improvements in imaging studies, tumor focus cannot be detected in 12-19% of patients with EAS[6]. In our first case, radiological scanning was performed with suspicion of EAS and a pulmonary nodule was detected. In the PET-CT, which was taken due to the presence of a different lesion, metastasis and metabolic status, no other foci showing FDG involvement or any suspicious findings in terms of metastasis were detected. However, in our second patient, ectopic ACTH focus was detected in the thorax CT performed after 2 years of follow-up.

The management of EAS patients is to control hypercortisolism at the time of diagnosis.

Therefore, glucocorticoid synthesis inhibitors are used[7]. Potassium replacement and spironolactone are used to control hypokalemia. Lowering cortisol levels before surgery is crucial in reducing mortality and morbidity[8]. When an ectopic ACTH source is detected, surgery is the first option in treatment, if possible. The 10-year survival rate has been reported as 82-87%, and recurrence has been reported as 3%[9]. We considered surgery as the first option since the clinical conditions of the patients were convenient for the operation. After wedge-resection of the lesions, it was reported as carcinoid tumor for both in the frozen-pathological evaluation. Lobectomy and mediastinal lymph node dissection were performed in both patients. No tumor metastases were detected in the lymph nodes. The immunopositive staining of the tumors for chromogranin, synaptophysin and ACTH supported that our diagnosis of EAS originated from these tumors. In postoperative period, rapid decrease of serum ACTH and morning cortisol levels was detected (Figure 4a-b).

Both patients were considered as complete remission after curative resection with normalization of cortisol levels in the post-operative period, the patients' normotensive and normokalemic course, and the regression of hypercortisolism findings during the follow-up period.

CONCLUSION

It is possible to achieve excellent long-term survival rates and control hypercortisolism caused by EAS by surgical resection in patients with suitable clinical conditions.

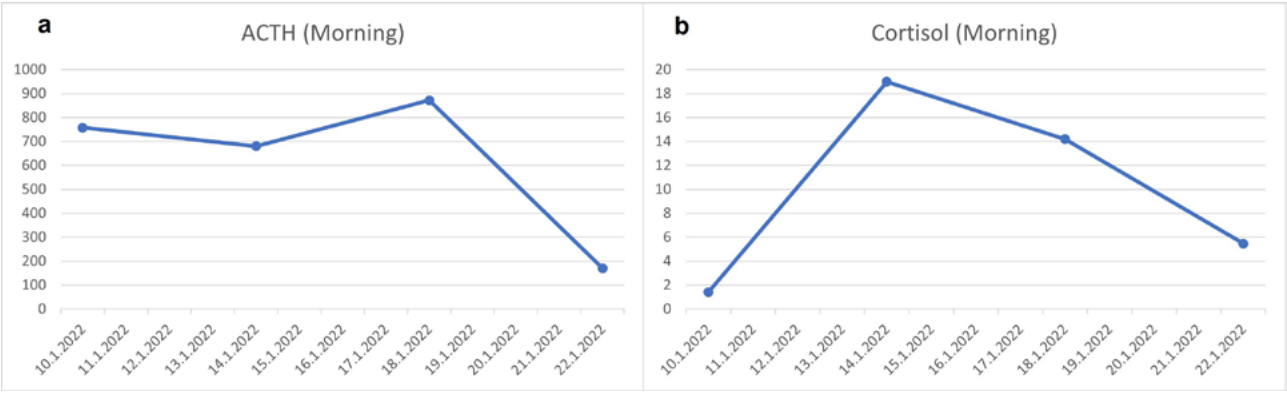

Figure 4 *Graphics show a rapid decrease in serum ACTH levels (4a) and morning cortisol levels (4b) of patients after surgical removal of ectopic focus.*

REFERENCES

1. 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 2005,90:4955-4962.
2. Newell-Price J, Bertagna X, Grossman AB, et al. Cushing's syndrome. Lancet 2006;367:1605-1617.
3. Bhansali A, Walia R, Rana SS, et al. Ectopic Cushing's syndrome: experience from a tertiary care centre. Indian J Med Res 2009;129:33-41.
4. Meador CK, Liddle GW, Island DP, et al. Cause of Cushing's syndrome in patients with tumors arising from "nonendocrine" tissue. J Clin Endocrinol Metab 1962;22:693-703.
5. Fazel P, Ganesa P, Mennel RG & Austin NA. The ectopic adrenocorticotropic hormone syndrome in carcinoid tumors. Proceedings 2008;21:140-143.
6. Cannon J, Doherty G. A case of occult ectopic adrenocorticotropic hormone- secreting tumor: diagnostic and management dilemmas. Endocr Pract 2008;14:588–591.
7. Yang HJ, Sung HJ, Kim JE, Lee HJ, Park JM, Park CK, et al. A case of ectopic ACTH syndrome associated with small cell lung cancer presented with hypokalemia. J Korean Endocr Soc 2007;22:359-64.
8. Ejaz S, Vassilopoulou-Sellin R, Busaidy NL, Hu MI, Waguespack SG, Jimenez C, et al. Cushing syndrome secondary to ectopic adrenocorticotropic hormone secretion: The University of Texas MD Anderson Cancer Center Experience. Cancer 2011;117:4381-4389.
9. Singer J, Werner F, Koch CA, Bartels M, Aigner T, Lincke T, Fasshauer M, Paschke R: Ectopic Cushing's syndrome caused by a well differentiated ACTH-secreting neuroendocrine carcinoma of the ileum. Exp Clin Endocrinol Diabetes 2010,118:524-529.