Ectopic Cushing's Syndrome due to Thymic Neuroendocrine Tumor Treated with Surgery and Radiotherapy

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ABSTRACT

The most common cause of ectopic Cushing's syndrome is small cell lung cancer; less common causes include pancreatic and thymic neuroendocrine tumors. A 35-year male was investigated after detecting low potassium in the tests performed for weakness. The patient was admitted for exclusion of Cushing's syndrome because of high cortisol (108 µg/dl) and ACTH (827ng/L) levels. There was no suppression in the high-dose dexamethasone test, and the patient was thought to have ectopic Cushing's syndrome. A mass in the thymus was detected in thorax tomography. Postoperative ACTH and cortisol levels decreased rapidly. Postoperatively, ACTH did not drop to normal, suggesting the possibility of residual tumor. Radiotherapy was given to the patient because the surgical margin was positive in the pathology report. No functional focus was detected in Ga 68 DOTATATE PET CT after radiotherapy. This case is presented because of the rare association of a thymic neuroendocrine tumor with ectopic Cushing's syndrome, which was revealed during the investigation of the etiology of hypokalemia.

Key Words: *Hypokalemia, Cushing syndrome, Thymic neuroendocrine tumor.*

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INTRODUCTION

Cushing's syndrome is a rare disease in which the consequences of glucocorticoid excess are observed. This syndrome may present with various clinical manifestations. It is most commonly seen as weight gain, central obesity, uncontrolled diabetes, hypertension, osteoporosis, muscle weakness, skin changes, hirsutism, and infertility. The most common cause is exogenous due to chronic steroid use. The most common causes of endogenous Cushing's syndrome are ACTH-secreting pituitary adenomas (Cushing's disease), which account for 60-70% of patients, and adrenal Cushing's syndrome for 20-25%. Tumors with paraneoplastic syndromes associated with secretion of ectopic ACTH and CRH are responsible for the rest of the cases of ectopic Cushing's syndrome. The most common cause of ectopic Cushing's syndrome is small cell lung cancer; less common are pancreatic and thymic neuroendocrine tumors (NETs).[1,2]

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This case is presented because it is a case of ectopic Cushing's syndrome caused by a thymic typical carcinoid tumor, which was detected incidentally when the patient consulted for muscle weakness and low potassium and was investigated.

CASE REPORT

A 35-year male patient presented at another centre with complaints of weakness and muscle pain. The anterior pituitary hormones of the patient were investigated after low TSH and fT4 levels were detected. The patient was referred to us with high levels of cortisol (108 ug/dl) and ACTH (827 ng/ml). The patient was admitted to the endocrinology ward. On physical examination, there were ecchymoses on the abdomen and moon-like face. Electrocardiogram was in sinus rhythm, blood pressure was 130/80 mmHg, and pulse was 75/min. Routine biochemical and anterior pituitary hormones tests were repeated (Table I). Intravenous and oral potassium supplementation was initiated for the patient's hypokalemia. Levothyroxine treatment was started. Spironolactone was added to the treatment as potassium levels remained low during the follow-up. The dose was gradually increased up to 250 mg. The cortisol rhythm was considered corrupted. There was no suppression in basal cortisol after a single dose of 1 mg and a high dose dexamethasone suppression test. Twenty-four-hour urinary cortisol was high. In the magnetic resonance imaging of the pituitary, the pituitary gland height was about 3 mm. Hypophysis was observed homogeneously in non-contrast and contrast-en-

hanced sections. No adenoma was detected, and the neurohypophysis was normal. Pituitary stalk and optic chiasm were also normal. Adenohypophysis volume was reported to be slightly decreased in relation to the age of the patient. Thoracic CT showed a mass lesion of approximately 25×19 mm in the anterior mediastinum (Figure 1), and on abdominal CT, diffuse thickening was detected in both adrenal glands. The patient was referred to a thoracic surgeon for considering surgical excision of the thymic tumor. The patient had thrombocytopenia on admission. The coagulation tests were normal. The patient was evaluated by hematology. No fragmentation was found in the peripheral smear. Total blood count was monitored. The patient became disoriented in time and place along with difficulty in communication. Brain imaging of the patient was done. The presentation of the patient was attributed to organic psychosis due to cortisol elevation. Positron emission tomography (PET) was done before surgery. No additional pathology was found except for the mass in the thymus. The mass was excised with a median sternotomy. Postoperative ACTH and cortisol values are shown in Table I. The patient was started on intravenous hydrocortisone treatment because of low cortisol and the development of hypotension. In the follow-up, the patient's potassium and platelets improved. The patient was discharged with oral hydrocortisone 30 mg and was advised to gradually decrease the steroid dose. Gross and histopathological examination of the surgical specimen showed a solid mass lesion, 2×2×2 cm in size, in a 5×4×3 cm tissue sample originating from the thymus adjacent to the surgical margin, and it was reported as the thymic typical carcinoid tumor (Pan CK focal +, chromogranin A +, synaptophysin -, CD56 +, p63 -, CD34 -, CD5 -, Ki-67 index 2%, ACTH +) (Figure 2A,B). One week later, steroid dose was gradually reduced and stopped. A 1 mg dexamethasone suppression test was performed and it was found to be suppressed. The patient was also evaluated by medical oncology and radiation oncology due to the presence of tumour at the surgical margin. Conventional radiotherapy was given to the patient. DOTATATE Ga-68 PET CT was performed at 6th month follow-up after radiotherapy. There was no relapse or recurrence. Multiple endocrine neoplasia type 1 (MEN-1) genetic tests were negative.

DISCUSSION

Thymic tumors constitute only 2-5% of NETs. A thymic primary site accounts for approximately 0.4% of all carcinoid tumors.

The largest reported series of thymic NETs comprised 160 patients who were reported in the Surveillance, Epidemiology, and End Results (SEER) database over a 33 years period. The median age at presentation was 57 years, and the male to female ratio was 3:1. The disease was confined to the thymus, locally invasive (or involving regional lymph nodes), or distantly metastatic in 27, 36, and 28% of cases, respectively.[3]

Up to 25% of thymic NETs arise in patients with MEN-1, which is a genetic disorder that predisposes to the development of multiple endocrine and non-endocrine proliferations. Although rare, thymic NETs represent neoplasms with greater malignant potential than other MEN-1-associated tumours, and therefore, they are an important cause of morbidity and mortality in MEN-1 kindred.[4] In this case, MEN-1 genetics is negative.

Table I: Laboratory results of the patient.

	Preoperative	Postoperative	Reference range
Glucose	92	80	70-100mg/dl
Blood Urea Nitrogen (BUN)	13	13	6-20 mg/dl
Creatinine	0.71	0.79	0.67-1.17 mg/dl
AST*	50	23	0-35 U/L
ALT*	21	15	0-45 U/L
Sodium	141	139	136-146 mEq/L
Potassium	2.7	4.6	3.5-5.1 mEq/L
Total leucocyte count	9.66	8.69	4.8-10.8 X10^3/µL
Hemoglobin	11.9	10.1	12-17 g/dl
Platelet count	61	442	130-400 x 10^3/µL
Growth Hormone	0.07	0.05	<3 µg/L
IGF-1*	65.9	76	115-307 µg/L
FSH*	1.12	4.13	1.27-19.26 IU/L
LH*	1.17	2.43	1.24-8.62 IU/L
Testosterone	2.37	1.89	1.98-6.79 µg/L
ACTH*	827	28.6	<46 ng/L
Cortisol	108	17.23	
TSH*	0.26	1.62	0.41-6.80 mIU/L
T4*	0.42	1.3	0.57-1.24 ng/dl
Prolactin	11.48	14.15	2.64-13.13 µg/L

**AST: Aspartate transaminase, ALT: Alanine transaminase, IGF-1: Insulin-like growth factor, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, ACTH: Adrenocorticotropic hormone, TSH: Thyroid-stimulating hormone, T4: Thyroxine.*

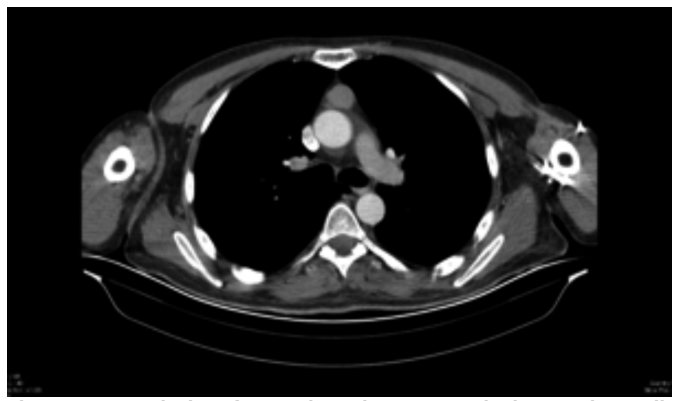

Figure 1: A mass lesion of approximately 25×19 mm in the anterior mediastinum on computed tomography).

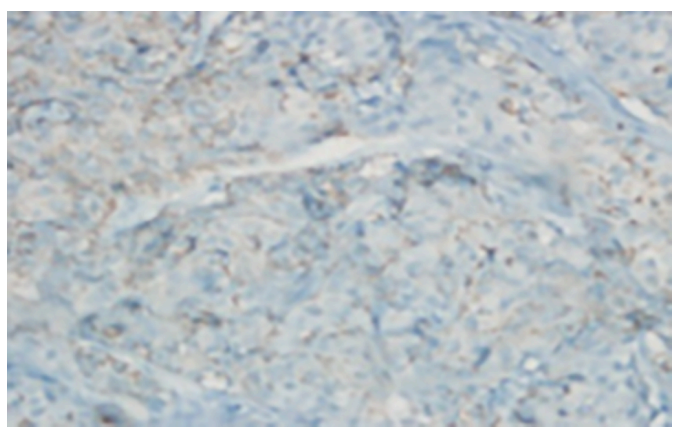

Figure 2(A): Weak granular cytoplasmic ACTH positivity is seen in the neoplasm (IHC, x400).

Pathological classification of NETs arising in the thymus include low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or high-grade (large cell neuroendocrine carcinoma, small cell carcinoma) tumours.[5] In this case, the patient's tumour was low-grade.

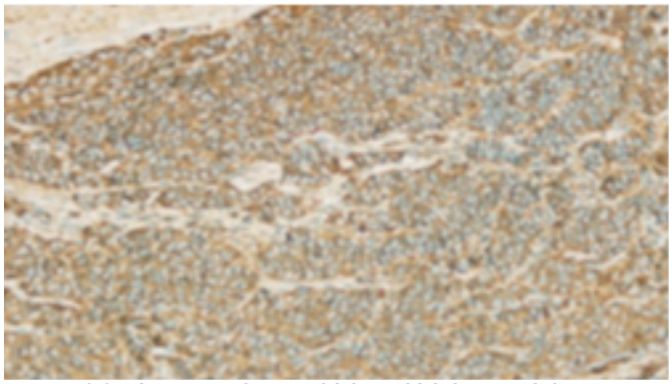

Figure 2(B): Chromogranin a positivity, which is one of the neuroendocrine markers, is seen in the neoplasm (IHC, x200).

Thymic NETs can be aggressive neoplasms with a tendency to invade adjacent structures. Many are locally invasive at the time of diagnosis, and mediastinal lymph node metastases are present in approximately 50% of patients at presentation.[6] This patient had no distant metastases at the time of diagnosis.

In older series, a clinically apparent endocrinopathy was found in up to one-half of cases of patients with thymic carcinoids. The most common is Cushing's syndrome due to ectopic production of ACTH.[7]

If the diagnosis of a thymic NET is established on biopsy, the evaluation should be completed with cross-sectional imaging of the abdomen and baseline somatostatin receptor imaging using either gallium Ga-68 DOTATATE PET/CT, or indium-111 pentetreotide (OctreoScan).[8]

Given the aggressive behavior of many thymic neoplasms, 18-F fluorodeoxyglucose (FDG) PET scans may be useful for initial staging and monitoring of disease activity in patients with poorly differentiated tumors and/or to further characterise negative or equivocal somatostatin-receptor-based diagnostic imaging.[9]

Surgery is the upfront treatment method in NETs of the thymus. Median sternotomy is performed in most cases. The results of radiotherapy, chemotherapy, or combined therapy in thymic carcinoids have not been fully evaluated. These modalities do not significantly contribute to the recurrence rate or survival. In addition, postoperative radiotherapy helps to prevent local recurrence in invasive carcinomas.[10]

Surgery was performed on this patient and radiotherapy was started due to positive surgical margins.

Most patients have local recurrence within 5 years after surgery. The prognosis is directly dependent on the degree of differentiation of the tumor. Five-year survival is approximately 50% in well-differentiated thymic carcinoids, 25% in moderately differentiated and 0% in poorly differentiated ones.[6]

In conclusion, ectopic Cushing's syndrome is a rare disease and may present in different clinical forms. Thymic carcinoid tumour should also be kept in mind in patients with suspected ectopic Cushing's syndrome.

PATIENT'S CONSENT:
Informed consent was obtained from the patient.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
YEG: Concept, design and writing.
IN: Critical review and supervision.
SVK: Literature review.
SE: Data collection and processing.
DT: Design.
All authors approved the final version of the manuscript to be published.

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