North Clin Istanb
doi: 10.14744/nci.2018.53244

Case Report Thoracic Surgery

UNCORRECTED PROOF

Ectopic Cushing's syndrome due to acth secreting atypic thymic carcinoid tumor

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ABSTRACT

Cushing's syndromes (CS) due to thymic carcinoids are rarely seen. In this text, a case with CS due to ectopic ACTH secreting atypical thymic carcinoid tumour is presented. A 50- year-old Turkish male patient was admitted to our emergency department with typical CS features. Basal hormone profile, low and high dose dexamethasone suppression tests, and inferior petrosal sinus sampling results were consistent with ectopic ACTH secretion. Thorax CT showed an upper mediastinal mass and transthoracic biopsy showed atypical thymic carcinoid with positive ACTH staining. Because the vascular invasion was detected, tumour was accepted inoperable; somatostatine receptor analogues, chemotherapy and radiotherapy were planned. Ectopic CS can be derived from atypical thymic carcinoid. In this case, ACTH staining was used to confirm ACTH secretion from thymic tissue and positive staining was detected. ACTH staining routinely was not performed for extra hypophyseal tissue tumours. In suspicious and difficult cases, ACTH staining can be helpful to confirm the presence of ACTH in tumour tissues.

Keywords: Ectopic Cushing's syndrome; thymus; carcinoid tumour.

Cite this article as: *Duran C., Eren Karanis M. I., Bakdik S., Aslan U., Calik M., Goknil Calik S. Ectopic cushing's syndrome due to acth secreting atypic thymic carcinoid tumor. North Clin Istanb*

Cushing's syndrome (CS) due to ectopic adrenocorticotropic hormone (ACTH) and corticotrophin releasing hormone (CRH) secretion from non-pituitary tumours comprise of 10–20% of all endogen CS [1, 2]. In clinical basis, these tumours can be divided into two main groups, tumours those are more malignant such as small cell lung tumours and less malignant tumours such as neuroendocrine tumours or carcinoids [2]. Thymic carcinoids account for less than 5% of all carcinoid tumours and1% of all cases with endogen CS [3, 4]. Thymic carcinoids are classified as typical and atypical. The latter is more aggressive than thypicalone and shows microscopically more necrosis and mitoses [5, 6]. Contrary to malignant tumours, like small cell tumours of lung, such patients either have typical clinical and biochemical symptoms and/or signs of CS; so differential diagnosis may be difficult in the distinction of Cushing's disease from these indolent causes of ectopic ACTH secreting CS [7, 8].

In this text, a case with CS due to ectopic ACTH secreting atypical thymic carcinoid tumour is presented.

Received: April 13, 2017 *Accepted:* February 01, 2018 *Online:* August 07, 2018

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Table 1. The results of basal hormonal levels and after suppression tests

Basal serum cortisol (N----------µg/dl)	32.8
Plasma ACTH (N----------pg/ml)	257.9
24 h. Urine cortisol level (N: 36–137 µg/day	953
Low dose overnight DST (1 mg/day) (µg/dl)	22
High dose DST (8 mg/day) (µg/dl)	25.34
Cortisol levels at 00.00 (µg/dl)	18.62
Cortisol level at 01 am. (µg/dl)	22.0
Cortisol level at 07 am. (µg/dl)	20.69

ACTH: Adrenocorticotropic hormone; DST: Dexamethasone suppression test.

Table 2. Plasma ACTH levels before and after CRH administration during inferior petrosal sinus sampling test

Sampling times	Right	Left	Peripheral
Basal	196.6	230	310.3
1st minute	310.5	244.6	236
3rd minute	259.4	222.8	296.9
5th minute	228.2	269.2	243.8
15th minute	230.8	216.7	209.1

ACTH: Adrenocorticotropic hormone; CRH: Corticotrophin releasing hormone; Results are given as pg/ml.

CASE REPORT

A 50-year-old male patient was admitted to our emergency department with the complaint of fatigue and weight loss (nearly 8 kg for the last 2 years). In his history, he had hypothyroid and hypertensive for three years and treated with l-thyroxine, candesartan 16 mg with hydrochloride 12.5 mg in combination, and amlodipin 5 mg per day. On his physical examination, he was 180 cm in height and 80 kg in weight, body mass index was 24.6 kg/m^2, blood pressure was 130/80 mmHg. He had central obesity, plethora, acne, moon face and dorsal fat pad. Chest X-ray showed upper mediastinal widening. Considering CS, 24-h urine free cortisol, plasma ACTH and serum cortisol were measured and found as 953 µg/day (normal 36–137 µg/day), 257.9 pg/ml and 32.8 µg/dl, respectively. Low dose overnight dexametasone suppression test (DST) and high dose DST (8 mg) were unable to suppress serum cortisol levels (22 µg/dl and 25,34 µg/dl, respectively). Diurnal rhythm was accessed

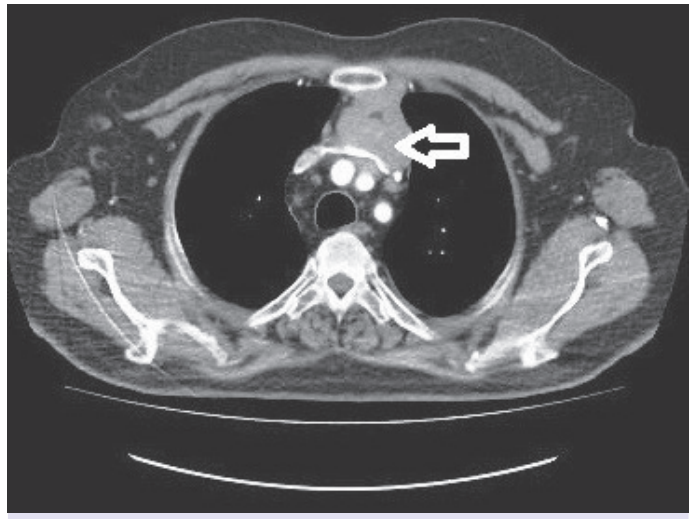

Figure 1. Axial thorax computerized tomography showed a macrolobulary mass (White arrow) with irregular border and calcification, invasion to brachio-cephalic vein and pathological size paratracheal, subcarinal and hiler lymphadenopathy.

and serum cortisol levels were found as 18.62 µg/dl, 22.0 µg/dl and 20.69 µg/dl at 00 00, 01 00 and 07 00, respectively and considered abnormal (Table 1). Sella magnetic resonance imaging (MRI) was normal. Inferior petrosal sinus sampling was performed and right-to-left ACTH ratio was found lower than 1.4. After the CRH administration central to peripheral ACTH ratio was found lower than 2, and these results were related with ectopic Cushing's syndrome (Table 2). Because he had upper mediastinal widening, thorax computerized tomography was performed and showed a macro lobular mass in size of 67x49 mm with irregular border and calcification, and also invasion to brachio-cephalic vein and paratracheal, subcarinal and hilar lymphadenopathy in a size up to 45 mm were detected (Figure 1). Transthoracic tri-cut biopsy was performed and pathological examination revealed atypical thymic carcinoid. Microscopically, tumour was composed of uniform cells with nested, trabecular and rosette-like growth patterns. Polygonal tumour cells have moderate eosinophilic granular cytoplasm, round to oval nuclei, "salt and pepper" chromatin and inconspicuous nucleoli (Figure 2a). Focal necrosis and two mitosis per high power field (HPF) were seen. "Dot-like" staining pattern was detected with immune histochemical Pan-CK stain. Tumour cells were positive with immune histochemical ACTH, Synaptophysin and Chromograin staining (Figure 2 b, c). Chromogranin A (Cg A) levels were found <5 ng/ml. Positron Emission Tomography

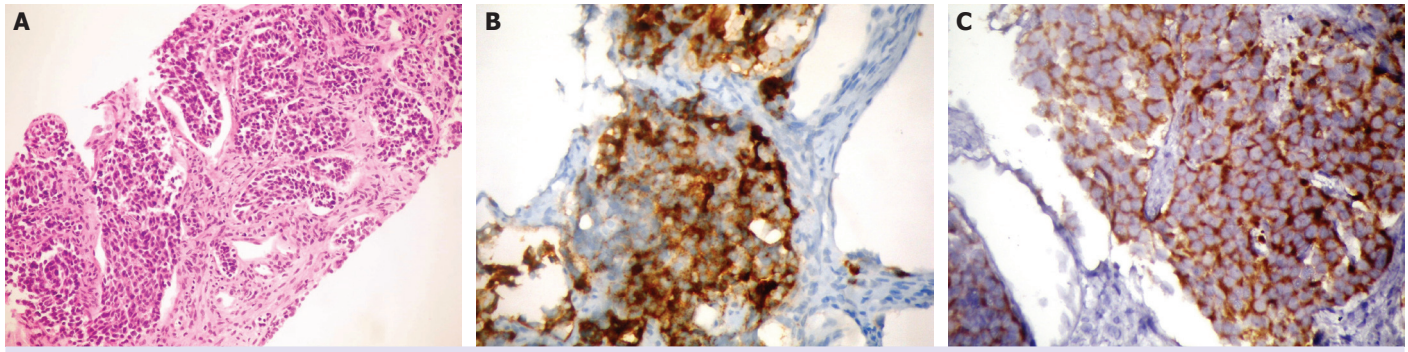

FIGURE 2. (A) Atypical carcinoid. Uniform tumor cells with nested, trabecular and rosette-like growth patterns. Polygonal tumor cells have moderate eosinophilic granular cytoplasm, round to oval nuclei, "salt and pepper" chromatin and inconspicuous nucleoli. (H&E staining, 200× magnification) H&E x200. (B) Immunohistochemical staining with ACTH. (ACTH staining, 400× magnification) ACTH x400. (C) Immunohistochemical staining with Synapthopysin. (Synapthopysin staining, 400× magnification) Synapthopysin x400.

and Computerized Tomography (PET/CT) revealed an increased FDG uptake (SUV max: 11.99) in the mass and in lymphadenopathy (SUV max: 7.76). With these findings, the patient was accepted as CS due to ACTH-secreting thymic carcinoid. Considering the patient inoperable, cisplatin (75 mg/m^2), etoposide (100 mg/m^2), somatostatin receptor analogues (SRA) and radiotherapy treatment were planned.

DISCUSSION

In this report, a case with CS due to ectopic ACTH secreting atypical thymic carcinoids is presented. Neuroendocrine tumours of the thymus are classified as typical carcinoid, atypical carcinoid and neuroendocrine carcinoma (large cell neuroendocrine carcinoma and small cell neuroendocrine carcinoma) [9]. Criteria to distinguish these tumours are based on mitoses and necrosis. Atypical carcinoid can be diagnosed bifocal necrosis and/or 2 to 10 mitoses per 10 HPF is detected in a neuroendocrine tumour [9]. Main pathological differential diagnosis of atypical thymic carcinoid are metastatic low grade neuroendocrine carcinoma, thymic epithelial tumour with neuroendocrine differentiation, paraganglioma and type A thymoma [9]. Atypical thymic carcinoids are more aggressive than typical ones and survival rate is low [5, 6, 10]. Another clinical importance of carcinoids is that it can be complicated by endocrine abnormalities. ACTH secretion from thymic carcinoid is a very rare condition and has been described only in limited numbers [1–3, 7, 8, 11–13]. ACTH-dependent CS may result from ectopic ACTH production; and, it is usually difficult to distinguish from hypophyseal - ACTH secretion. Underlying slow growing tumour, such as carcinoids, can mimic Cushing's disease. Rarely can these tumours be cyclic secretuar and to carry out dynamic endocrine tests during this period is often inconclusive. Additionally, most of these tumours are occult and it is difficult to detect the source of ACTH production [14]. In this case, higher plasma ACTH levels and no suppression were detected during low and high dose DST. IPSS was compatible with ectopic ACTH secretion and thorax CT revealed a thymic mass, as we considered ectopic ACTH syndrome due to thymic cancer, biopsy was performed and atypical carcinoid was detected. To confirm the ACTH source from this tissue, ACTH staining was performed and positive staining was detected. Despite the fact that, chromogranin is a useful marker for the diagnosis and follow-up of neuroendocrine tumors (NETs), serum Cg A levels were determined normal in our case. In a recently published review, the sensitivity, specificity, PPV and NPV was reported 84.2%, 78.2%, 41.5% 96.4% respectively in the NET diagnosis of Cg A. For this reason, it is important to remember that normal Cg A levels in NETs are not always guiding [15].

Treatment options of thymic carcinoids are surgical excision, chemotherapy, SRA and radiotherapy. Due to aggressivity of the atypical carcinoid tumour, lesions are commonly diffuse and multifocal; therefore, surgical cure can be achieved only in limited patients. Likewise, although different chemotherapy regimens are recommended, success rate is lower than 30% [16]. In a recent study of 30 patients with thymic NET, 5 and 10-year survival was determined as 77% and 30%, respectively,

and it was reported that survival was better in patients whose tumour was [17]. New anticancer drugs success rates seem to increase much more. Crona et al. reported the efficacy of temozolomide or platinum-based chemotherapy as median time in the first treatment of 28 patients with high Ki 67 index or thymic carcinoid resected wholly macroscopically as 20.5 and 18 months, respectively [18].

As carcinoid tumours have expressed somatostatin receptors, SRA can be used for suppression of tumour growth and ectopic hormone secretion [19]. In addition, somatostatin receptor scintigraphy (SRs) can help to distinguish thymic pathologies from simple thymic hyperplasia and to show distant metastases [20]. However, we could not do SRs due to technical inadequacies. In our case, because of vascular invasion and multiple lymphadenopathy, surgery was not preferred for initial therapy instead lanreotide, cisplatin and etoposide treatments were started and conventional radiotherapy was planned.

In conclusion, ectopic CS can be derived from atypical thymic carcinoid. In this case, we used ACTH staining in thymic tissue to confirm ACTH secretion from these tissues and positive staining was detected. Routinely, ACTH staining was not performed for extrahypophysial tissue tumours. In difficult cases, ACTH staining can be helpful to confirm the presence of ACTH secretion in tumour tissues.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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