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Case Report Thoracic Surgery

Ectopic Cushing's syndrome due to adrenocorticotropic hormone secreting atypical 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 adrenocorticotropic hormone (ACTH) secreting atypical thymic carcinoid tumor 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 computerized tomography showed an upper mediastinal mass, and trans-thoracic biopsy showed atypical thymic carcinoid with positive ACTH staining. Since the vascular invasion was detected, tumor was accepted inoperable; somatostatine receptor analogs, 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 tumors. In suspicious and difficult cases, ACTH staining can be helpful to confirm the presence of ACTH in tumor tissues.

Keywords: Ectopic Cushing's syndrome; Carcinoid tumor; thymus.

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Cushing's syndrome (CS) due to ectopic adrenocorticotropic hormone (ACTH) and corticotrophin-releasing hormone (CRH) secretion from non-pituitary tumors comprise 10–20% of all endogen CS [1, 2]. In clinical basis, these tumors can be divided into two main groups, tumors those are more malignant such as small cell lung tumors and less malignant tumors such as neuroendocrine tumors or carcinoids [2]. Thymic carcinoids account for <5% of all carcinoid tumors and 1% of all cases with endogen CS [3, 4]. Thymic carcinoids are classified as typical and atypical. The latter is more aggressive than typical one and shows microscopically more necrosis and mitoses [5, 6]. Contrary to malignant tumors, like small cell tumors 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 tumor is presented.

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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 past 2 years). In his history, he had hypothyroid and hypertensive for 3 years and treated with l-thyroxine, candesartan 16 mg with hydrochloride 12.5 mg in combination, and amlodipin 5 mg/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 dexamethasone 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). The diurnal rhythm was accessed, 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 was normal. Inferior petrosal sinus sampling was performed, and the 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 CS (Table 2). Since he had upper mediastinal widening, thorax computerized tomography (CT) was performed and showed a macro lobular mass in size of 67 mm × 49 mm with irregular border and calcification, and also invasion to brachiocephalic vein and paratracheal, subcarinal and hilar lymphadenopathy in size up to 45 mm were detected (Fig. 1). Transthoracic tri-cut biopsy was performed, and pathological examination revealed atypical thymic carcinoid. Microscopically, tumor was composed of uniform 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 (Fig. 2). Focal necrosis and two mitoses per high power field (HPF) were seen. "Dot-like" staining pattern was detected with immune histochemical Pan-CK stain. Tumor cells were positive with immune histochemical ACTH, synaptophysin, and chromogranin staining (Fig. 2). Chromogranin A (Cg A) levels were found <5 ng/ml. Positron emission tomography and CT revealed an increased FDG uptake (SUV max: 11.99)

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 min	310.5	244.6	236
3rd min	259.4	222.8	296.9
5th min	228.2	269.2	243.8
15th min	230.8	216.7	209.1

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

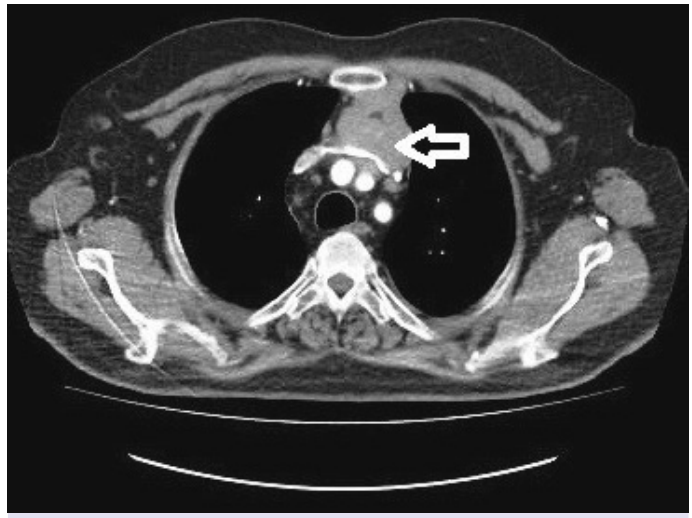

Figure 1. Axial thorax computerized tomography showed a macrolobulary mass (white arrow) with irregular border and calcification, invasion to brachio-cephalic vein and pathological size paratracheal, subcarinal, and hilar lymphadenopathy.

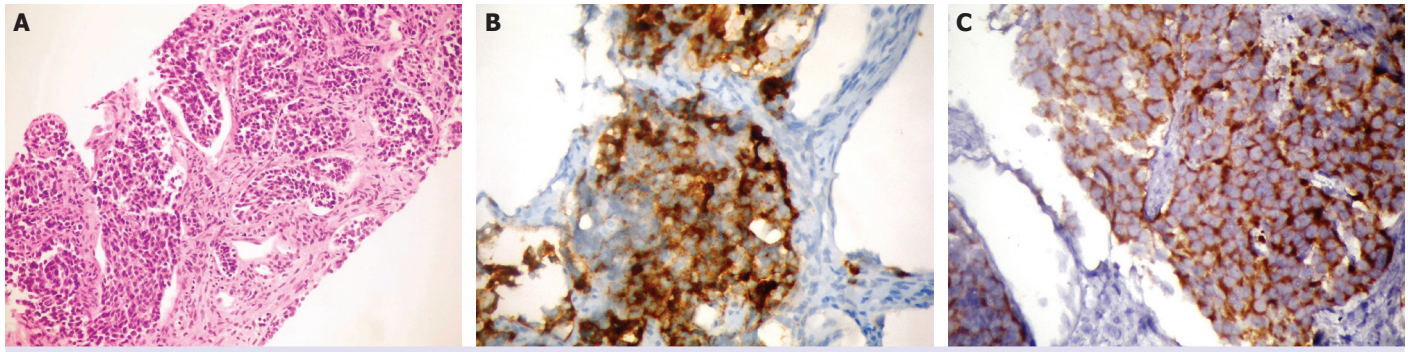

FIGURE 2. (A) Atypical carcinoid. Uniform tumor cells with nested, trabecular and rosette-like growth patterns. Polygonal tumor cells have moderate eosinophilic granular cytoplasm, round to oval nuclei, "salt and pepper" chromatin and inconspicuous nucleoli (H&E staining, ×200 magnification) H&E ×200.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

in the mass and 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 analogs (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 tumors (NETs) 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 tumors are based on mitoses and necrosis. Atypical carcinoid can be diagnosed with bifocal necrosis and/or 2–10 mitoses per 10 HPF is detected in a NET [9]. Main pathological differential diagnosis of atypical thymic carcinoid is metastatic low-grade neuroendocrine carcinoma, thymic epithelial tumor with neuroendocrine differentiation, paraganglioma, and type A thymoma [9]. Atypical thymic carcinoids are more aggressive than typical ones, and the 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 tumor, such as carcinoids, can mimic Cushing's disease. Rarely can these tumors be cyclic secretary and to carry out dynamic endocrine tests during this period is often inconclusive. In addition, most of these tumors 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, a 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, Cg is a useful marker for the diagnosis and follow-up of NETs, serum Cg A levels were determined normal in our case. In a recently published review, the sensitivity, specificity, positive predictive value, and negative predictive value were reported 84.2%, 78.2%, 41.5%, and 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 tumor, lesions are commonly diffuse and multifocal; therefore, the surgical cure can be achieved only in limited patients. Likewise, although different chemotherapy regimens are recommended, the success rate is <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 tumor was [17]. New anticancer drugs success rates seem to in-

crease 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 tumors have expressed somatostatin receptors, SRA can be used for suppression of tumor 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, due to vascular invasion and multiple lymphadenopathies, surgery was not preferred for initial therapy instead of lanreotide, cisplatin, and etoposide treatments were started, and conventional radiotherapy was planned.

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 tumors. In difficult cases, ACTH staining can be helpful to confirm the presence of ACTH secretion in tumor 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.

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