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# Atypical carcinoid tumor of the thymus: two case reports

*Timusun atipik karsinoid tümörü: İki olgu sunumu*

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Carcinoid tumors of thymus originating from neuroendocrine cells of thymus are seen very rarely. It is three times more in male. Clinically, thymic atypical carcinoid tumor demonstrates a more aggressive course than thymic typical carcinoid tumor. The disease-free survival rate is usually worse. The primary choice of treatment is extended resection which should be achieved tumor-free resection margins. The efficacy of radiotherapy and chemotherapy is still unclear. In this article, we present two cases who had atypical carcinoid tumor with adrenal insufficiency in one and Cushing disease in other.

*Key words:* Carcinoid tumor; thoracic surgery; thymus.

Timusun nöroendokrin hücrelerinden köken alan timusun karsinoid tümörlerine çok nadir rastlanır. Erkeklerde üç kat daha fazla görülür. Klinik olarak timik atipik kasinoid tümörler, tipik karsinoid tümörlerden daha agresif bir davranış sergiler. Hastalıksız sağkalım oranı genellikle kötüdür. Tedavide birinci seçenek, tümörsüz rezeksiyon sınırlarının elde edildiği geniş rezeksiyondur. Radyoterapi ve kemoterapinin etkinliği halen belirsizdir. Bu yazıda, birinde adrenal yetmezliğin, diğerinde ise Cushing hastalığının eşlik ettiği atipik karsinoid tümörlü iki olgu sunuldu.

*Anahtar sözcükler:* Karsinoid tümör; göğüs cerrahisi; timüs.

The gastrointestinal tract and lungs have been accepted as the origins of carcinoid tumors since Rosai and Higa first reported the neuroendocrine tumor of the thymus in 1972.[1-3] Thymic carcinoid tumors (TCTs) are rare and represent only 4% of all anterior mediastinal tumors.[1] In addition, carcinoid tumors are seen three times more in men than in women.[1] Herein, we report two cases with atypical carcinoid tumors. One patient had adrenal insufficiency, and the other had Cushing's disease.

## CASE REPORT

***Case 1–*** A 22-year-old man was admitted to our department in May of 2006 complaining of difficulty in breathing. He had been diagnosed with hypertension, Cushing's syndrome, and a thymic mass and had been followed up for 19 months by the rheumatology department for seronegative arthritis. After the development of hypertension and Cushing-like symptoms, he was referred to the endocrinology department. Thorax computed tomography (CT) verified the thymic mass. A transthoracic needle biopsy was performed, and the pathological findings showed a thymic neoplasia. He was then referred to thoracic surgery department for surgery for the thymic mass.

A physical examination detected only a moon face and increased blood pressure (160/100 mmHg) while laboratory examination revealed elevated levels of adrenocorticotropic hormone (ACTH) (75.18 pg/mL, normal range 0-46 pg/mL), cortisol (63.44 microgram/dL), lactate dehydrogenase (861 U/lt, normal range 200-450 U/lt), and urine cortisol (1776.75 microgram/24 h in 1500 cc urine). Tumor markers were within the normal range. All of these findings were concordant with Cushing's syndrome. A computed tomography (CT) scan of the thorax showed that a relatively well-contoured,

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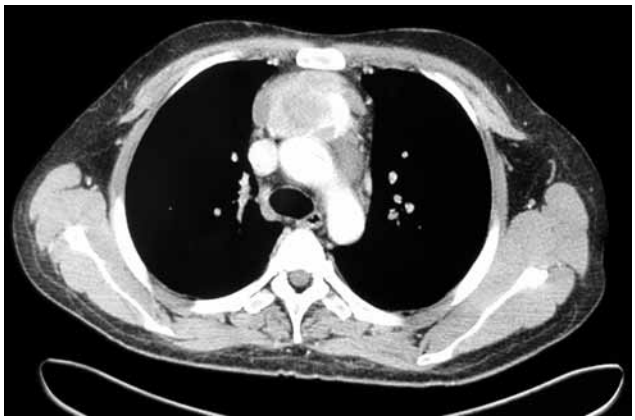

**Figure 1.** Thoracic computed tomography scan of case 1.

lobulated mass measuring 6x5x6 cm which had calcifications in patches, located on the aortic arch (Figure 1). Brain magnetic resonance imaging (MRI) showed a 4 mm microadenoma located at the middle and posterior right side of the pituitary gland.

Surgical resection was performed by a median sternotomy in May 2006, and the mass and surrounding fatty tissue were resected together. The pathological examination revealed an atypical carcinoid tumor arising from the thymus (Figures 2a, b).

Cyclophosphamide 500 mg/m$^2$ intravenous (i.v), doxorubicin 50 mg/m$^2$ i.v, and cisplatin 50 mg/m$^2$ i.v were given to the patient on day one and repeated every 21 days in order to complete three cycles. The patient had no recurrence of the disease at the three-year follow-up.

***Case 2–*** A 49-year-old man was admitted to our department in April of 2009. He had been followed up for adrenal insufficiency, which had been under control for six years, and had been under evaluation for three months in the pulmonary disease department to determine the etiology of a persistent cough. A mediastinal mass was determined on thoracic CT. A transthoracic needle biopsy was performed, and a thymic epithelial neoplasia was determined during a pathological examination. The patient was then referred to thoracic surgery department for surgical resection of the thymic mass.

On his physical examination, there were no abnormal findings, and a laboratory examination revealed normal levels of ACTH (36.6 pg/mL) and cortisol (7.48 microgram/dL) along with elevated levels of alpha-fetoprotein (AFP) (6.62 IU/ml, normal range 0-5.8 IU/ml). All of these findings were concordant with adrenal insufficiency. The thoracic CT showed a

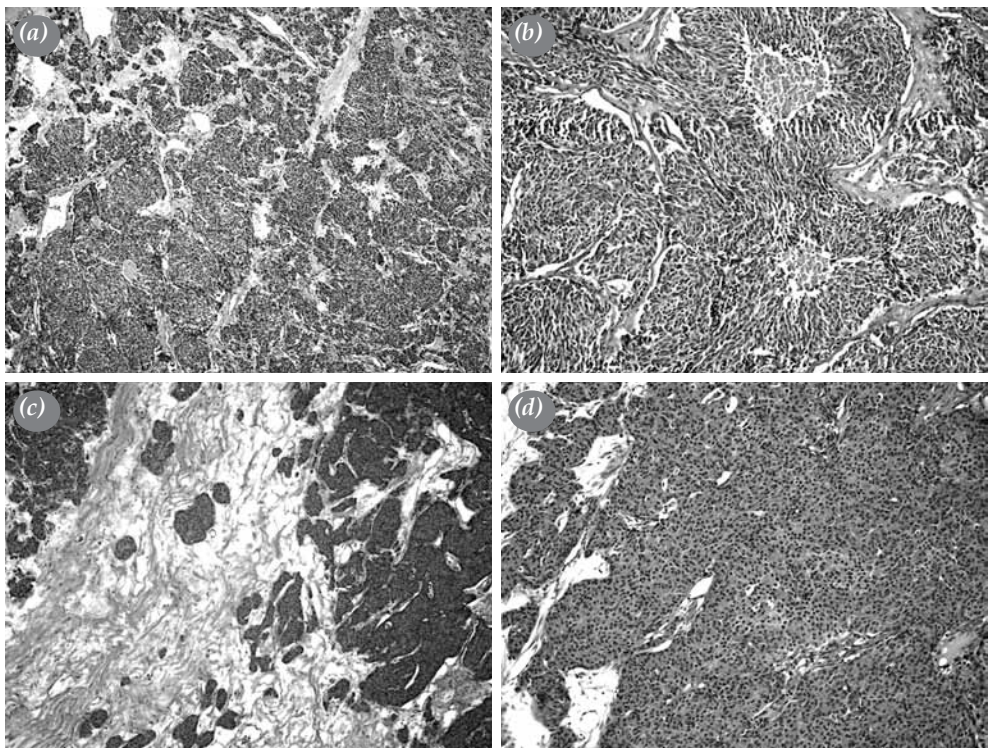


**Figure 2. (a)** Solid tumor nests separated from fibrous septa (H-E x 40). **(b)** Area of comedonecrosis (H-E x 200). **(c)** Tumor islands in edomatous stroma (H-E x 40). **(d)** Large polygonal tumor cells with oxyphilic cytoplasms (H-E x 100).

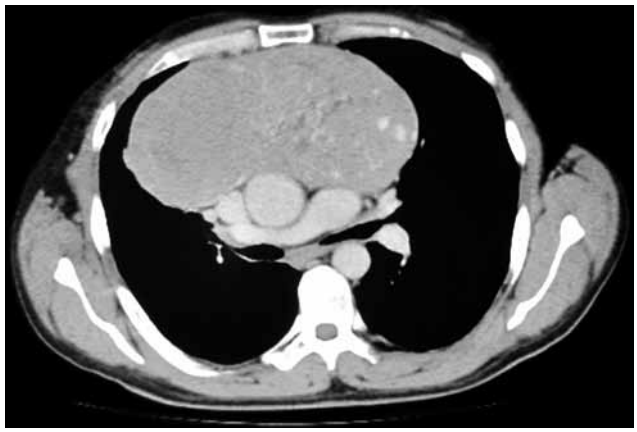

**Figure 3.** Thoracic computed tomography scan of case 2.

relatively well-contoured mass measuring 19x12x10 cm originating from the anterior mediastinum (Figure 3).

Surgical resection was performed by a median sternotomy in May of 2009. The mass and the surrounding fatty tissue were resected concommitantly. The pathological examination of the tumor showing areas of necrosis and high mitotic activity revealed an encapsulated atypical carcinoid tumor with an oncosytic variant arising from the thymus with invasions through the soft tissue (Figures 2c, d).

Cyclophosphamide 500 mg/m$^2$ i.v, doxorubicin 50 mg/m$^2$ i.v, and cisplatin 50 mg/m$^2$ i.v were prescribed to the patient on the first day and were repeated for 21 days to complete three cycles. Nine months after the surgery, multiple abdominal metastases were detected.

## DISCUSSION

Carcinoid tumors arise from neuroendocrine cells,[4] and it is very rare to find them in the thymus. They have an estimated incidence of 3/10,000,000 people a year.[5,6] Approximately 250 patients with TCTs had been reported as of 2009,[7] and they account for approximately 2% of all carcinoid tumors that arise from various organs.[2] In addition, TCTs occur three times more frequently in males[1] and are most commonly seen in the fifth decade of life.[2] Our two cases were male.

Clinically, atypical TCTS demonstrate a more aggressive course than typical ones.[8] Unlike bronchial carcinoids, carcinoid tumors behave aggressively and usually recur and generate widespread metastases.[1] Rapid progression and metastases occurring within one to three years after diagnosis is common.[1] However, in case 2, multiple abdominal metastases were detected only nine months after surgery. Furthermore, the disease-free survival rate is shorter with TCTS,[9] and the patients are usually asymptomatic.[10] Detection of a mass is usually achieved via routine chest X-ray, but it can also be detected due to symptoms connected with the localized compression effects of the mass or those associated with endocrinopathy[1,2] The patient in case 1 was admitted to our department because of symptoms related to paraneoplastic syndrome, whereas the patient in case 2 was admitted due to the mass effect of the tumor. Approximately 30-40% patients with TCTs have Cushing's syndrome secondary to the production of ACTH, the most common endocrine product made by these types of tumors.[1,3] Other endocrine products are antidiuretic and parathyroid hormones.[1] In our cases, one patient had Cushing's syndrome, which is the most commonly seen endocrinopathy in neuroendocrine thymic tumors, and the other had adrenal deficiency, which to our knowledge has not been previously reported in the literature. Thymic carcinoid tumors are associated with multiple endocrine neoplasia (MEN) syndromes, especially MEN-1.[3] In our cases, no association with MEN syndromes was discovered. Like thymic

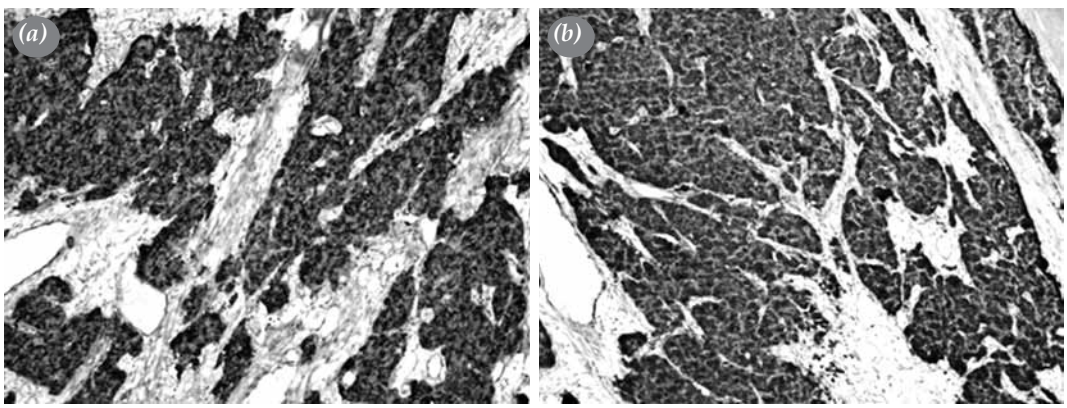


**Figure 4. (a)** Synaptophysin and **(b)** chromogranin reactivity in tumor cells (immunohistochemistry x 200).

carcinomas, TCTs tend to spread either lymphogenously or hematogenously[1] to the lungs, bones, adrenals, liver, or spleen.[6] Despite aggressive treatment, the 10-year survival rate is less than 50%, and patients with concommitant Cushing's syndrome have the lowest survival rate of 35% at five years.[6]

Thymic carcinoid tumors may be confused with epithelial thymomas, which have an entirely different prognosis.[10] The cytopathological diagnosis of our case 2 was thymic epithelial neoplasia.

Histologically, in addition to the typical carcinoid histopathological features (e.g., organoid features like ribbons, solid nests, glandular structures, and uniform round or oval polygonal cells with fine granular cytoplasms), atypical carcinoid tumors show areas of necrosis and/or high mitotic activity.[11] Endocrine differentiation is revealed by their reactivity to neuroendocrine markers such as synaptophysin, chromogranin, neuron-specific enolase, and CD56 via immunohistochemistry (Figures 4a, b).

A chest X-ray usually is not sensitive enough for diagnosis since the tumor may be superimposed by the mediastinal structures. Standard CT, MRI or standard CT, can confirm the presence or absence of a thymic tumor, but neither of these imaging techniques can distinguish the subtype of a thymic tumor. We diagnosed the mediastinal masses by performing standard CT imaging in both of our cases. Additionally, nuclear medicine studies may also be helpful if suspicious conditions exist. Octreotide scintigraphy is generally useful for identifying carcinoid tumors, but this imaging technique was not used in our cases. Although this type of scintigraphy is sensitive, it may not be specific.

Complete resection is the principal therapeutic modality, and it offers the best chance for a cure. An analysis made by Gal et al.[9] showed that unresectability, the extent of surgical resection, and advanced clinical stage were univariate factors associated with mortality. We performed *en bloc* ($R_0$) resection of the mediastinal masses, and the pathological surgery margins were tumor-free with a safe range.

Many authors emphasize that the efficacy of radiotherapy (RT) or chemotherapy (CHT) on thymic neuroendocrine tumors is still unclear, which could be because of their rarity. Gal et al.[9] showed that neither CHT nor RT made any difference in survival. Radiotherapy is usually administered as the primary therapy for unresectable tumors or as an adjuvant to resection,[1] and many authors have reported that it can achieve good local control.[7,9] It also may help to ameliorate the symptoms of paraneoplastic syndromes.[1] There is no standard regimen for CHT, and a wide variety of agents have been employed.[1] The patients in our cases were given cyclophosphamide, doxorubicin, and cisplatin for a three-cycle regimen by the oncology department. Octreotide therapy is a novel approach, and it may help slow tumor growth.[1] However, its use for treatment of patients with TCTs has not been reported,[1] and we used no biological therapy in our cases.

In conclusion, carcinoid tumors of the thymus gland tend to be associated with endocrinopathies, especially Cushing's syndrome, and the presenting symptoms are usually related to these connected diseases. While evaluating such endocrinopathies, thymic pathologies should be considered.

**Declaration of conflicting interests**

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