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Thymic carcinoid with multiple endocrine neoplasia type 1: a case report

Tip 1 multipl endokrin neoplazi ile timik karsinoid: Olgu sunumu

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Thymic carcinoid is a rare neuroendocrine tumor of the thymus. Apart from sporadic cases, it is usually associated with multiple endocrine neoplasia type 1 (MEN1). Thoracic computed tomography (CT) revealed an anterior mediastinal mass with a size of 10 cm in diameter, encroaching into the left thoracic cavity in a 39-year-old male case with MEN1-related giant thymic carcinoid who was admitted due to chest pain. A computed tomography-guided percutaneous tru-cut biopsy demonstrated a carcinoid tumor of the thymus. Tumor was resected through left thoracotomy. Pathologic analyses of the specimen revealed thymic carcinoid tumor, mostly encapsulated with local pericardial tissue invasion. The patient with familial MEN1 was asymptomatic for the past seven months. Thymic carcinoid is the leading cause of death in patients with MEN1 disease. Early diagnosis and treatment of this condition would help to minimize morbidity and mortality rate.

Key words: Multiple endocrine neoplasia; surgery; thymic carcinoid.

Timik karsinoid, timusun nadir görülen nöroendokrin tümörüdür. Sporadik olgular dışında, sıklıkla multipl endokrin neoplazi tip 1 (MEN1) ile ilişkilidir. Göğüs ağrısı yakınması ile başvuran ve dev timik karsinoid ile ilişkili MEN1 olan 39 yaşında erkek bir olguda, toraks bilgisayarlı tomografisinde (BT) çapı 10 cm olarak ölçülen sol göğüs boşluğuna taşan ön mediastinal kitle izlendi. Bilgisayarlı tomografi eşliğinde yapılan perkütanöz tru-cut biyopside timusun karsinoid tümörüne rastlandı. Tümör sol torakotomi ile çıkarıldı. Örneklerin patolojik incelemesinde sıklıkla lokal perikardiyal doku invazyonu ile kapsüle timik karsinoid tümöre rastlandı. Ailesel MEN1 izlenen olgu son yedi aydır asemptomatik idi. Timik karsinoid, MEN1 görülen olgularda başlıca ölüm nedenlerindendir. Erken tanı ve hastalığın tedavisi, morbidite ve mortalite risklerini en aza indirebilir.

Anahtar sözcükler: Multipl endokrin neoplazi; cerrahi; timik karsinoid.

Multiple endocrine neoplasia (MEN) is a group of benign and/or malignant tumoral lesions found in some endocrine tissues. A number of these tumors secrete hormones, but others do not. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant syndrome characterized by tumors of the parathyroid, the anterior pituitary, and gastroenterohepatic endocrine tissues. A diagnosis can be made if at least two of the three main endocrine tumors are present, and this syndrome has a prevalence rate in the general population of 0.01-2.5/100,000.[1] Genetic investigations have shown that MEN1 is caused by a defect in the menin gene on the long arm of chromosome 11 (11q13),[2] and the most common endocrinopathy associated with this syndrome is hyperparathyroidism (95-100%).[3]

Carcinoid tumors are seen in 10% of patients with MEN1, and they may originate from the thymus, bronchus, or gastroenterohepatic endocrine system. Thymic carcinoids tend to be more aggressive than other types of tumors and are the major cause of death in male MEN1 patients who smoke heavily.[4,5] Patients with hormone-secreting nonthymic carcinoids present at an early stage with Cushing's syndrome caused by adrenocorticotrophic hormone (ACTH) secretion.

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Nonsecreting thymic carcinoid tumors tend to grow larger and locally invade the surrounding tissues responsible for symptoms related mainly to tumor compression.[6] Various treatment options have been used to treat MEN1. External radiotherapy may be considered for patients with residue or recurrent tumor disease. In addition, since thymic carcinoids rarely respond to chemotherapy,[7,8] surgery is the treatment of choice for patients with a resectable thymic tumor with no extrathoracic metastasis.

CASE REPORT

We report the case of a 39-year-old male patient who was admitted to another hospital with loss of libido and gynecomastia as the initial symptoms five years prior to coming to our facility. At that time, investigations revealed a prolactin level of 3722 ng/ml (normal range, 0-15 ng/ml), and cranial computed tomography (CT) revealed an adenoma in the hypophysis region. Furthermore, magnetic resonance imaging (MRI) revealed a 40x37x30 mm hypophyseal adenoma compressing on the right optic nerve, which was also surrounding the basilar artery. Moreover, there was bilateral cavernous invasion, especially on the left side. The patient was prescribed 15 mg daily bromocriptine mesylate (Parlodel), but this was discontinued after one month due to dysphagia. He then underwent a craniotomy to remove the hypophyseal adenoma because he was experiencing headaches and weight loss. The removed specimen was confirmed to be prolactinoma. After the surgery, the patient had a prolactin level of 397 ng/ml and normal triiodothyronine (T_3), tetraiodothryonine (T_4), thyroid-stimulating hormone (TSH), plasma testosterone, ACTH, and plasma cortisol levels. He was also asymptomatic postoperatively. At the one-year follow-up, he had hypercalcemia with calcium levels of 14.2 mg/ml (normal range: 8.4-10.2 mg/ml), which prompted a neck ultrasound that revealed a parathyroid adenoma. A right total parathyroidectomy was subsequently performed. In addition, an upper gastrointestinal (GI) system endoscopy for dyspepsia that had not responded to medical treatment was conducted, which showed ulcerated plaques in the third part of the duodenum and jejunum. The patient's gastrin level was 550 pg/dl (normal range, 10-150 pg/ml). He was then diagnosed with gastrinoma and put on proton pump inhibitor (PPI) therapy,

The patient, who had been asymptomatic for four years, was referred and admitted to our hospital after he started experiencing discomfort in the chest and palpitations. A diagnosis of MEN1 was made following the discovery of tumors in the three main endocrine regions, and family investigations revealed the presence of a parathyroid adenoma in his brother.

A physical examination showed evidence of the previous craniotomy and collar incision scars. The breathing sounds were reduced on the left side, and pericardial rub was present. Laboratory findings revealed elevated white blood cells (13200/μL), hyperglycemia (153 mg/dL), hypercalcemia (11.2 mg/dL), hypophosphatemia (2.1 mEq/L), and elevated alkaline phosphatase (133 IU/L). However, the T_3, T_4, and TSH levels were normal. Chest CT revealed a 13x9x11 cm mass with a lobulated contour in the superior mediastinum that was encroaching into the anterior superior chest wall of the left hemithorax along with signs of left main pulmonary artery compression (Figure 1). Positron emission tomography (PET) and CT revealed a large mass measuring 14.6x10.7x11.9 cm with rough edges that extended from the upper middle mediastinum to the left lateral thoracic wall. It also occupied a large area of the hemithorax with increased activity [standardized uptake value (SUV) max: 8.97], and additional increased activity was also noted in the right parietal cortex (SUV max: 10.28) along with a pathological intake in the right adrenal gland and pathological intakes in the tail of the pancreas. Abdominal CT revealed hypodense lesions with calcification that measured 13 mm and 19 mm in diameter, respectively. Furthermore, there was a thin layer of tissue (possibly a pseudocyst or a macrocystic adenoma) in the tail of the pancreas together with a 20x17 mm lesion in the right adrenal gland (Figure 2). A cranial MRI revealed lesions measuring 10x10x10 mm and 21x16x14 mm lesions in the right and left sphenoid, respectively. Most probably these were part of the same lesion, and it was extending bilaterally into the cavernous sinus. Neurosurgeons attributed the cranial lesions to a recurrent, residual hypophyseal

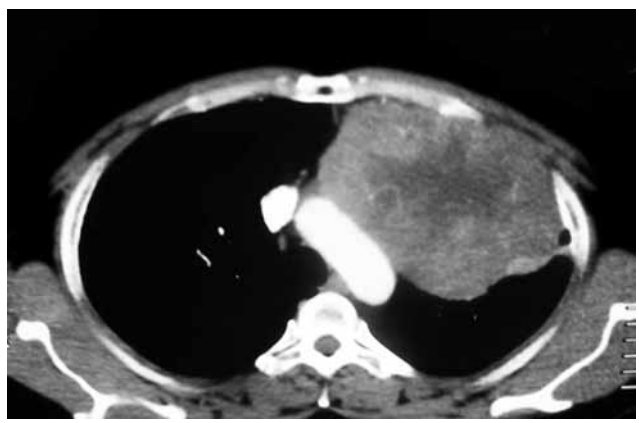

Figure 1. Computed tomographic scan revealing a mass anterior to the aortic arch.

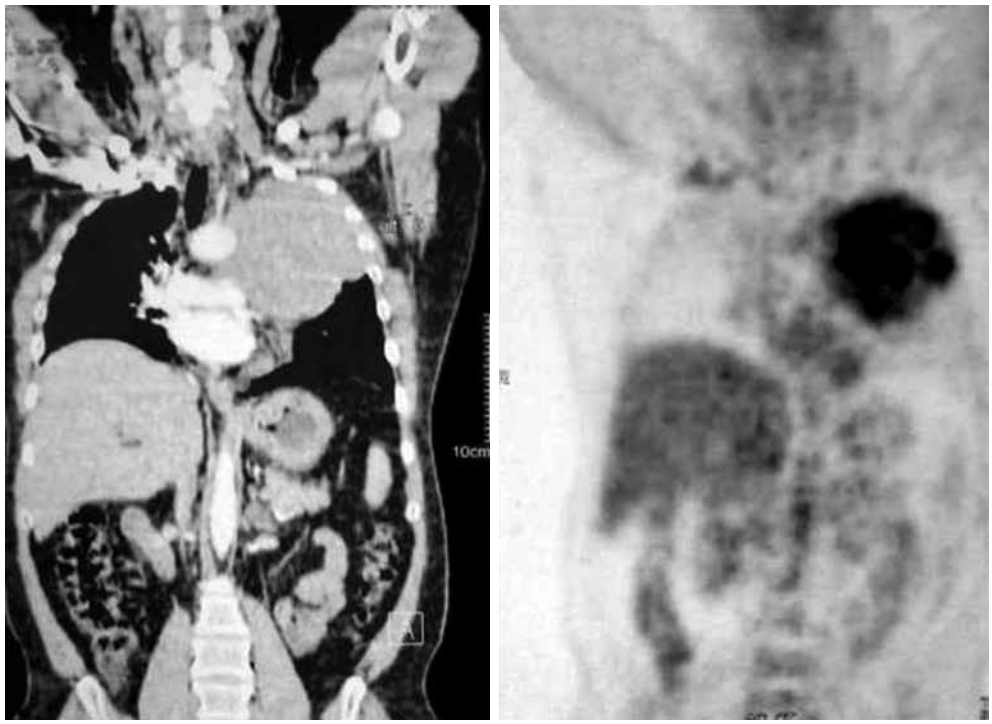

Figure 2. Positron emission tomographic scan of the patient.

adenoma secondary to the surgery; hence, no further surgical procedure was required. An echocardiogram revealed signs of compression on the pulmonary artery as well as minimal mitral and tricuspid failure in conjunction with normal left ventricle functions.

A transthoracic biopsy was positive for a carcinoid tumor, and the patient, who had no extrathoracic metastasis and a resectable lesion, was operated on via a left thoracotomy. The tumoral mass was resected from the lung, thoracic wall, and left main pulmonary artery, and the brachiocephalic and subclavian arteries in the thoracic inlet were dissected. The tumor had affected a large part of the pericardium, but there was no cardiac invasion (Figure 3). It was removed en bloc after resection along the mediastinum and pericardium, and polypropylene mesh (Ethicon, a Johnson & Johnson company, Somerville, NJ, USA) was used to cover the large defect in the pericardium. In addition, lymph node sampling were done from the mediastinal and hilar lymph nodes adjacent to the tumor. The patient was discharged with no postoperative complications on the sixth postoperative day after the chest tubes were removed.

The pathology of the specimen was an atypical carcinoid tumor, which measured 14.5x13.5x10 cm and weighed 1,125 grams. Macroscopically, the tumor was noted to be mostly encapsulated. It had invaded the outer layer of the pericardium but had not penetrated the inner layer. Furthermore, the tumor had also invaded the neighboring thymus tissues, and three-four mitosis groups (per 10 HPF) were discovered. Moreover, the sample tested positive for immunohistochemical markers CD 56, chromogranin, neuronal-specific enolase (NSE), and 15-20% of Ki 67, but tests for the IgA-endomysial antibody (EMA) were negative (Figure 4).

No additional treatment was needed postoperatively, and the patient continued to be asymptomatic seven months after surgery.

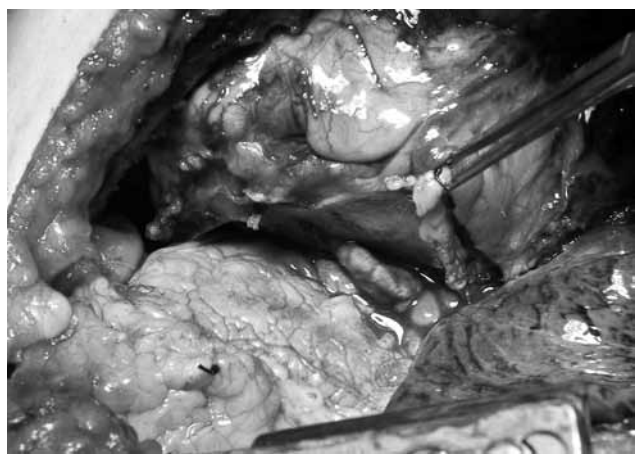

Figure 3. Intraoperative appearance of a lesion.

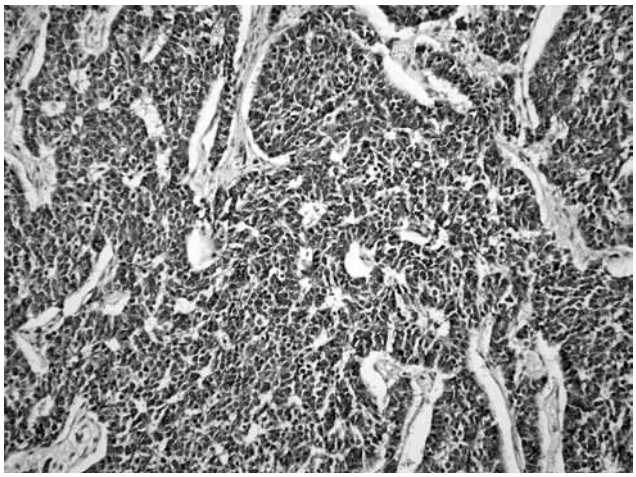

Figure 4. Immunohistochemical examination showing positive chromogranin in a thymic carcinoid tumor (immunoperoksidase x 200).

DISCUSSION

Multiple endocrine neoplasia type 1 is an autosomal dominant syndrome consisting of more than twenty different combinations of endocrine and nonendocrine tumors. It is generally characterized by parathyroid hyperplasia in 95-100% of patients, gastroenterohepatic endocrine tumors in 30-80%, and anterior pituitary tumors in 15-34%.[9] In addition, skin lesions, such as lipomas and angiomas, may be seen in 90% of patients with MEN1, and multiple adrenocortical tumors can be found in 15-34%. Furthermore, foregut (thymus, bronchial, and gastric enterochromaffin-like cells) carcinoids appear in 10-25% of patients with this disorder while pheochromocytoma and ependymoma are seen in only 1%.[10]

Familial MEN1 diagnosis requires at least one MEN1 case plus at least one first-degree relative with one of three of the main MEN1-related endocrine tumors.[11] In our case, the patient's brother had a parathyroid adenoma, thus fulfilling the requirements for diagnosis.

In 1972, Rosai et al.[12,13] were the first to describe primary neuroendocrine tumors in the thymus, and the authors subsequently discovered that they were associated with MEN1. In addition, Brandi et al.[11] determined that MEN1-related carcinoids are most commonly found in male patients who smoke and that these tumors often behave aggressively. Furthermore, it was determined that tumors related to MEN1 occur at an earlier age than sporadic tumors.[14] For example, the patient in our case was only 39 years old.

The most commonly noticed endocrinopathy is related to parathyroid tumors.[3] Patients present with hypercalcemia between the ages of 20 and 25, lethargy, depression, confusion, constipation, diuresis, dehydration, renal stones, increased bone resorption, and the risk of bone fracture in the fifth decade of life.[15] Prolactinoma of the pituitary gland presents as oligomenorrhea and/or amenorrhea along with galactorrhea in female patients, whereas males have symptoms of sexual dysfunction.[16] In fact, the initial complaints of our patient were sexual dysfunction and gynecomastia. Further investigations then revealed a pituitary adenoma (prolactinoma). Gastroenterohepatic tumors may present as Zollinger-Ellison syndrome (gastrinoma), hypoglycemia (insulinoma), hypercalcemia, anorexia, anemia, diarrhea, venous thrombosis (glucagonoma), hypokalemia, or achlorhydria [vasoactive intestinal peptide (VIP)-secreting tumors].[16] Our patient was diagnosed with gastrinoma after experiencing dyspeptic symptoms which did not respond to medical treatment.

Most patients are asymptomatic until the late stages of MEN1, but some present with chest pain and discomfort.[14] Thymic carcinoid tumors are primarily diagnosed in the late stage of the syndrome; thus, they present with a large, invasive mass. Our patient was asymptomatic until the encroachment of the large tumor size began to cause symptoms.

The sensitivity of CT and MRI is similar when evaluating the presence of and follow-up for the recurrence of thymic carcinoids.[11] The lower sensitivity of chest X-rays and somatostatin receptor scintigraphy (SRS) versus CT and MRI was reported by Gibril et al.,[6] who suggested avoiding the use of SRS scans in the first line of investigation. In our case, a chest X-ray revealed only the enlarged mediastinum while chest CT was helpful in determining the size of the tumor, the level of encroachment into the hemithorax, and the resectability of the mass.

The main treatment option for localized or locoregional thymic carcinoid tumors is the surgical resection of the primary tumor and intrathoracic lymph node metastasis.[17] A median sternotomy is the preferred method when an extended total thymectomy and complete tumor resection are required along with peripheral tissue removal and mediastinal lymph node sampling.[18] However, it is appropriate to use a thoracotomy for very large carcinoids in the mediastinum that are encroaching into the hemithorax. In these cases, an additional sternotomy may also be required. In our case, a larger part of

the tumoral mass was in the left thoracic cavity, and pericardial invasion was present, necessitating a left thoracotomy.

Some authors have suggested performing a prophylactic thymectomy during a parathyroidectomy for primary hyperparathyroidism in order to reduce the risk of thymic carcinoid tumors, especially in male patients.[19,20] Our patient had undergone a parathyroidectomy with no thymus gland resection four years previously. Filosso et al.[21] were the first to use the multidisciplinary treatment approach of neoadjuvant chemoradiotherapy, radical resection, and hormonal therapy (octreotide). They also advocated the benefits of examining serum chromogranin-A levels for disease follow-up and recurrence as well as the investigation of the patient's response to the octreotide therapy.

Carcinoids rarely respond to etoposide and cisplatin chemotherapy.[3] Most recently, somatostatin analogs like octreotide (Sandostatin® LAR®, Novartis International AG, Basel, Switzerland) and tyrosine kinase inhibitors like sunitinib malate [Sutent® (previously known as SU11248), Pfizer Inc., New York, NY, USA] have been used in the treatment of neuroendocrine tumors such as thymic carcinoids.[8] In our case, further treatment was not required because a complete tumor resection was performed.

Brandi et al.[11] suggested that laboratory and radiological investigations should be carried out every three-five years and that the laboratory test should evaluate calcium, parathyroid hormone (PTH), gastric output, insulin, proinsulin, chromogranin A, glucagon, prolactin (PRL), and insulin-like growth factors. Thymic carcinoid tumors are often aggressive and invade adjacent structures, including the mediastinal fatty tissue, lungs, pericardium, and major vessels. Additionally, local recurrence and metastases are common;[21] hence, these patients have a poor prognosis. The median survival rate is reported to be 28 months, and the five-year survival rate is less than 30%.[22]

In conclusion, we believe that the early diagnosis and treatment of carcinoid tumors, the major cause of death associated with MEN1, would help reduce the morbidity and mortality rates of the patients afflicted with this syndrome.

Declaration of conflicting interests

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