A Case Report of Thymic Carcinoid Tumor Associated with Cushing’s Syndrome: Possible Corticotropin-Releasing Hormone Secreting Tumor

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Thymic carcinoid tumor associated with Cushing’s syndrome is a rare disease with a poor prognosis. Thymic carcinoid with Cushing’s syndrome caused by CRH (corticotropin-releasing hormone) production is even rarer. We report a 58-year-old woman with a huge anterior mediastinal mass. Five months after thymectomy the patient was readmitted with symptoms of generalized edema and dyspnea. Recurrence and metastases were discovered and Cushing’s syndrome diagnosed.

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Key words: 1. Thymus  
2. Thymectomy  
3. Carcinoid tumor  
4. Cushing’s syndrome

CASE REPORT

A 58-year-old woman was referred to our hospital for the investigation and treatment of a huge anterior mediastinal mass. Her initial symptoms were right chest pain, dyspnea, and palpitation. Computed tomography of her chest and a chest MRI revealed a 10×9×5.5 cm sized lobulated mass in her anterior mediastinum (Fig. 1). Moon face appearance was present initially, but was overlooked. A fine needle aspiration biopsy was performed to rule out possibility of lung origin and the biopsy revealed findings suggestive of thymoma. A left thymectomy was then performed.

A median sternotomy incision was done. A well-encapsulated large lobular mass containing dark blood-like fluid was bordered
Fig. 1. Chest CT reveals 10 x 9 x 5.5 cm sized solid and heterogeneous mass with multiple lymphadenopathy. The mass is located in the anterior mediastinum and is attached to the aortic arch, pericardium, and anterior chest wall.

superiorly by her left innominate vein, medially by aortic arch, inferiorly by pericardium, laterally by mediastinal pleura and left upper lobe. The mass was relatively well encapsulated and was moderately adhered to her pericardium, surrounding fat tissue, and left innominate vein. There was no adhesion to the lung. Frozen sections revealed suspected lymphocytic thymoma. Partial thymectomy was performed because of the seemingly benign nature, being well encapsulated and cystic.

Gross examination presented a lobular and encapsulated mass and the cut surface revealed a partly solid and a partly cystic region showing areas of hemorrhage and necrosis. On histologic examination, there was residual thymic tissue with Hassall’s corpuscles and small lymphocytes adjacent to the tumor. The tumor was highly cellular and revealed solid nests and trabecular pattern compartmentalized by delicate fibrovascular stroma (Fig. 2A). In the periphery of the mass, the tumor cells also formed ribbon-like or Indian file appearance. Lymphatic tumor emboli were frequently seen. The tumor cells were uniform and had granular eosinophilic cytoplasm. The nuclei were round with stippled powdery chromatin and inconspicuous nucleoli. Mitotic figures were occasionally seen. The tumor cells were positive for cytokeratin, neuron specific enolase, synaptophysin, and chromogranin, but negative for ACTH (Fig. 2B). Histopathologically, the tumor was diagnosed as atypical carcinoid tumor of the thymus.

The patient was discharged on her postoperative 16th day and received postoperative radiotherapy at 5,000 rads one month later.

Five months later the patient developed symptoms of generalized edema and dyspnea. A chest CT revealed progression of tumor invading her pericardium and involvement of her right paratracheal lymph nodes. She also had shown direct invasion of her left phrenic nerve, presenting left hemidiaphragmatic elevation. She was readmitted and found with high ACTH levels and a positive dexamethasone suppression test (high dose). Her free serum cortisol and plasma ACTH levels were 829 μg/day and 103 pg/mL. The patient’s T3, free T4, and TSH levels were within the normal range. The patient’s urinary 17-OHCS levels were surprisingly suppressed by 8 mg of dexamethasone from 103 to 73 pg/mL. Following administration of 100 μg ovine CRH intravenously, blood ACTH actually decreased from 158 to 137 pmol/L (45 min). The response of cortisol levels to CRH was blunted (did not increase) from 23.6 to 21.6 nmol/L (45 min). Brain MRI had shown no signs of a pituitary lesion.

The patient had then refused all treatment, except for simple pain control, and had expired 18 months after her initial operation.

DISCUSSION

Thymic carcinoid was first described in 1972 by Rosai and Higa[1] and since then over 150 cases have been reported. There have been reports of carcinoid tumor in Korea, but, none associated with Cushing syndrome[2,3]. Thymic carcinoid associated with Cushing’s syndrome is a rare event and only 25 cases have been reported in the English literature. Neuroendocrine carcinomas in the thymus account for 2 to 4% of all anterior mediastinal tumors[4]. There is only one other case in the English literature of a thymic carcinoid with Cushing’s syndrome caused by CRH production[5]. Clinically, adrenocorticotropic hormone (ACTH) production in thymic carcinoid is not uncommon. Our case caused much confusion and we believe a thorough study including studies for production of CRH in patients with thymic carcinoid and Cushing’s syndrome should be pursued. Such studies may prove to be an extremely important marker for recurrence or metastases.
Thymic carcinoid tumors associated with Cushing's syndrome occur from 4 to 64 years of age and peak between the second and fourth decades. There is no gender preference when associated with Cushing's syndrome[4]. Elevated cortisol serum levels or 24-hour urine levels confirm the diagnosis of Cushing's syndrome. A drop in the 24-hour urine and plasma steroids of more than 50% of base line after 8 mg of an oral dexamethasone suppression test indicates a pituitary origin of ACTH[4]. Our case had a negative dexamethasone suppression test and negative findings on her brain MRI; this would suggest an origin other than the pituitary. An intravenous CRH test revealed a blunted increase in blood ACTH concentration, suggesting ectopic secretion of CRH. Unfortunately, antisera for CRH within the removed thymic carcinoid itself was not available, but clinically, such results would suggest a thymic carcinoid tumor with ectopic CRH production.

Surgery is the treatment of choice and aggressive local resection, including the entire thymus and perithymic fat, is necessary[4]. Due to the aggressive nature and frequent metastases, postoperative radiotherapy is usually indicated to prevent local recurrence. Glucocorticoids during the surgical procedure and postoperatively are indicated due to the prolonged high cortisol levels, to prevent adrenal insufficiency during and after surgery[6]. In our case, the diagnosis of Cushing's syndrome was overlooked and thus, perioperative and postoperative doses of steroids were not given. Only after recurrence, was Cushing's syndrome diagnosed and ectopic secretion of CRH discovered.

Immunohistochemical analysis of thymic carcinoid usually stains positive with chromogranin A and synaptophysin. The diagnosis of a carcinoid tumor is further supported by the presence of neuron-specific enolase found in neuroendocrine cells of the amine precursor uptake and decarboxylation series[7]. ACTH usually is positive in those associated with Cushing's syndrome[4]. In our case, immunohistochemical studies for neuron specific enolase, chromogranin, and synaptophysin were positive, but ACTH was negative. As mentioned above, unfortunately, antisera for CRH could not be obtained in our country and ectopic secretion of CRH from a thymic carcinoid could only be suggested clinically.

The prognosis of thymic carcinoid is very poor and most patients will have local recurrence or metastasis within 5 years of surgery and expire within 10 years[4]. The five-year survival rate of thymic carcinoid has been reported to be 13% and the average survival at 3 years[8]. We believe a total thymectomy and postoperative adjuvant therapy may have prolonged her survival. It was unfortunate that there was a discrepancy between preoperative, intraoperative and postoperative pathologic reports. Again, when Cushing's Rosai J, Hig syndrome associated with thymic carcinoid is encountered, a thorough study of not only ACTH, but also studies for CRH should be performed, especially in cases where a negative
study for ACTH is found.

REFERENCES


=국문 초록=

쿠성 증후군과 연관된 흉신 carcinoid 종양은 드문 질병으로 그 예후가 나쁜 것으로 알려져 있다. 그 중 부신과절자극 호르몬 분비 촉진 호르몬을 생산하는 흉신 carcinoid 종양은 흔히 더 드물다. 우리나라의 대한 전방 중앙동 종양을 갖고 있는 58세 여자 환자에 대해 보고하려고 한다. 환자는 흉신재건술 5개월 후 전반적인 부종과 호흡곤란으로 다시 입원하였다. 환자는 재발과 전이가 발견되었고 루성 증후군으로 진단 받았다.

중심 단어 : 1. 흉신
2. 흉신재건술
3. Carcinoid 종양
4. 루성 증후군