Korean J Thorac Cardiovasc Surg 2012;45:60-64 □ Case Report □
ISSN: 2233-601X (Print) ISSN: 2093-6516 (Online) http://dx.doi.org/10.5090/kjtcs.2012.45.1.60

Large Cell Neuroendocrine Carcinoma of the Thymus: A Two-Case Report

Yong Han Yoon, M.D.[1], Jae Ho Kim, M.D.[1], Kwang Ho Kim, M.D.[1], Wan Ki Baek, M.D.[1], Hyun Kyu Lee, M.D.[2], Moon Hee Lee, M.D.[2], Kyung Hee Lee, M.D.[3], Lucia Kim, M.D.[4]

A large cell neuroendocrine carcinoma (LCNEC) of the thymus is a very rare malignant tumor that has a very poor prognosis. The detailed clinical features of LCNEC are still unknown, including the long term prognoses and the definitive modalities of the treatment for LCNEC of the thymus. We are reporting 2 cases of an enlarged LCNEC of the thymus, both of which were diagnosed and treated by surgical resection followed by postoperative adjuvant chemoradiation therapy. Although recurrences and metastases of the LCNEC were noticed 1 and 4 years postoperatively for each case, aggressive surgical resection and adjuvant chemoradiation therapy may be helpful for a patient's long term survival.

Key words: 1. Tumor, malignant
2. Thymus
3. Large cell neuroendocrine carcinoma
4. Surgery

CASE REPORT

1) Case 1

A 64-year-old male patient was admitted due to a 1 month history of cough prior to admission. He had been relatively healthy except for hypertension for 10 years. He had smoked one pack of cigarettes every day for 30 years, but he had stopped smoking 5 years prior to admittance. A physical examination revealed no specific findings. All laboratory results were within the normal limits including carcinoembryonic antigen (CEA) levels. The chest posteroanterior (PA) radiograph (Fig. 1A) showed a large spherical mass obscuring the right heart border. A chest computed tomography (CT) (Fig. 1B) revealed a soft tissue mass in the right anterior mediastinum intertwined with the mediastinal fat. No fat plane was observed separating the mass from the ascending aorta. On transthoracic needle aspiration, the preoperative diagnosis was highly suspicious for a poorly differentiated carcinoma of the thymus. The preoperative Masaoka stage was stage III. A median sternotomy revealed that the mass (Fig. 2A) was well circumscribed, lobulated, grayish-yellow, and very hard, measuring 8.5×6.5×6 cm in size. The mass was located between the brachiocephalic vein and the diaphragm, and tightly adhered to the entire anterior pericardium, superior vena cava, ascending aorta, and the right upper lobe crossing the mediastinal pleura. A satellite mass 2 cm in diameter was located left of the brachiocephalic vein. The masses were removed with the anterior pericardium, including the right phrenic

Departments of [1]Thoracic and Cardiovascular Surgery, [2]Hematology and Oncology, [3]Diagnostic Radiology, [4]Pathology, Inha University Hospital, Inha University School of Medicine
Received: August 12, 2011, Revised: November 2, 2011, Accepted: November 11, 2011
Corresponding author: Kwang Ho Kim, Department of Thoracic and Cardiovascular Surgery, Inha University Hospital, Inha University School of Medicine, 7-206 Sinheung-dong 3-ga, Jung-gu, Incheon 400-711, Korea
(Tel) 82-32-890-2280 (Fax) 82-32-890-3390 (E-mail) khkim@inha.ac.kr

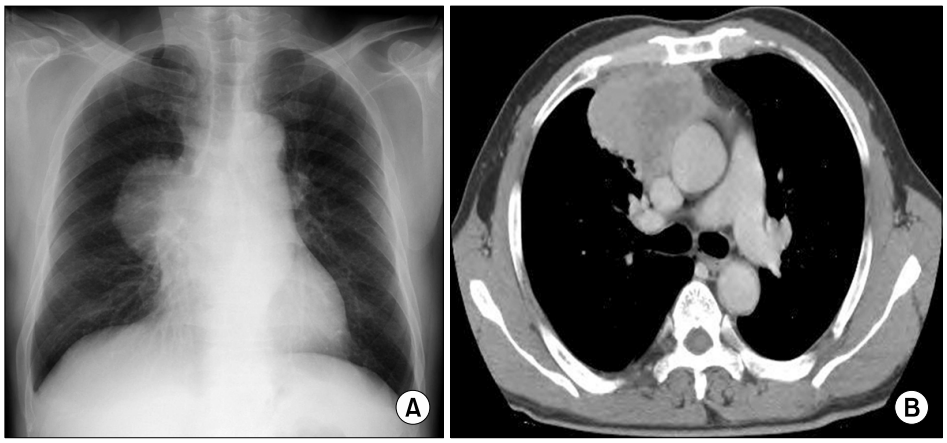

Fig. 1. (A) A chest radiograph of case 1 shows a large spherical mass obscuring the right heart border. (B) A chest computed tomography of case 1 reveals a soft tissue mass in the right anterior mediastinum invading the mediastinal fat. No fat plane is seen separating the mass from the ascending aorta.

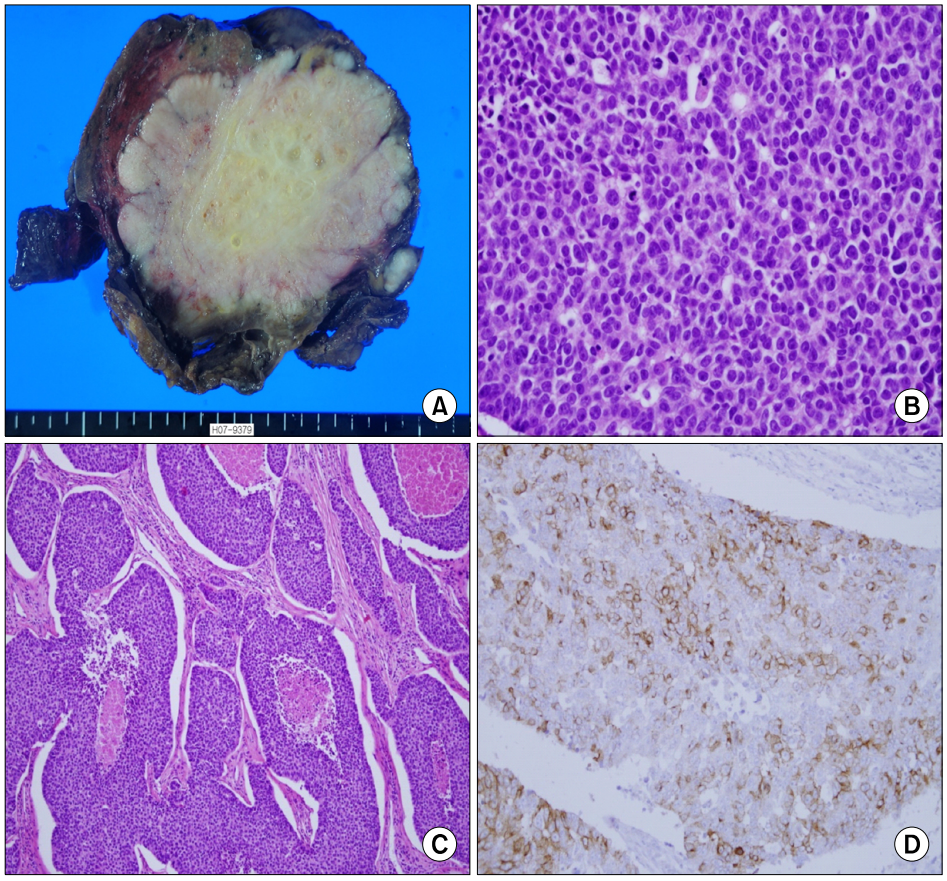

Fig. 2. (A) Gross findings of a large cell neuroendocrine carcinoma of case 1. The tumor is relatively well circumscribed and lobulated with a grayish-yellow, soft, solid, and granular cut surface. The tumor involves the adhered lung parenchyma and surrounding adipose tissue. Microscopic findings of a large cell neuroendocrine carcinoma of case 1. (B) The tumor is composed of irregularly-shaped solid nests with central necrosis (H&E, ×100). (C) The tumor cells show round nuclei, distinct nucleoli, a low nuclear-to-cytoplasmic ratio, frequent mitotic figures, and a rosette-like structure (H&E, ×400). (D) Some tumor cells are immunoreactive for the chromogranin immunohistochemical stain (chromogranin, ×200).

nerve and lymph nodes, avoiding injury to the great vessels. A wedge resection of the right upper lobe was performed. The final pathological report showed a large cell neuroendocrine carcinoma (LCNEC) of the thymus. The microscopic findings (Fig. 2B-D) showed the tumor was composed of irregularly-shaped solid nests with central necrosis. The tumor cells showed round nuclei, distinct nucleoli, a low nuclear-to-cytoplasmic ratio, frequent mitotic figures, and a rosette-like structure. The tumor cells were immunoreactive for the neuroendocrine markers chromogranin, synaptophysin, and CD57 on the immunohistochemical stains. The postoperative stage was Masaoka stage IVB due to a positive anterior me-

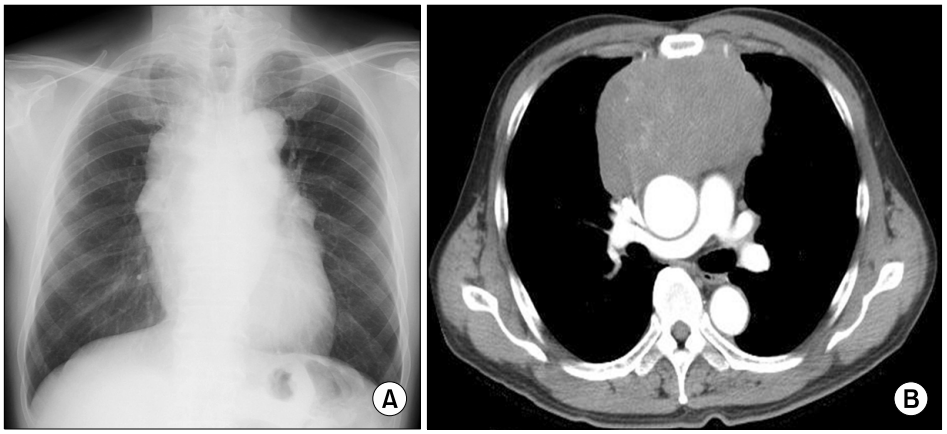

Fig. 3. (A) Chest radiograph of case 2 shows a bilateral lobulated large mediastinal mass. (B) Contrast enhanced computed tomography of case 2 shows a large anterior mediastinal mass with posterior displacement of the vascular structure. The mass encompasses the left internal mammary artery.

diastinal lymph node and invasion of tumor cells into the surrounding soft tissue. The patient's postoperative course was complicated due to a mediastinal infection by methicillin-resistant staphylococcus aureus. A vacuum-assisted closure was applied from postoperative day 21 to 36 and then the sternal wound was closed by bilateral pectoralis major muscle rotation flaps. He was discharged on postoperative day 88. The postoperative adjuvant chemoradiation therapy was postponed due to his poor general condition and the surgical wound condition. Radiation therapy was attempted with 4,500 cGy as soon as he developed superior vena cava syndrome one year later. However, metastases to the liver and left adrenal gland had been found 6 months after radiation therapy. Chemotherapy was attempted 12 times using a cisplatin 60 mg/m^2, adriamycin 40 mg/m^2, and cyclophosphamide 750 mg/m^2 regimen. The patient is still alive 4 years postsurgery although multiple metastases were noticed in his liver, in the left adrenal gland, and in the bone marrow.

2) Case 2

A 57-year-old male patient was admitted due to a known mediastinal mass that had been discovered by coronary computed tomography 6 months before this admission for the evaluation of exertional chest pain. He had been hypertensive for 5 years and received a left parotidectomy due to Warthin's tumor 5 years before admission. He was a 30-pack/year smoker, but he quit smoking 3 years prior to admittance. His physical examination was normal. His CEA level was normal. His chest PA (Fig. 3A) shows a bilateral lobulated large mediastinal mass. His chest CT (Fig. 3B) shows a large anterior mediastinal mass with a posterior displacement of the vascular structure. The mass encompassed the left internal mammary artery. A positron emission tomography scan showed no evidence of a distant metastasis. The mass was tentatively diagnosed as an atypical carcinoid tumor of the thymus by a transthoracic needle biopsy. Endeavoring to reduce the size of the huge mass, preoperative chemotherapy was attempted twice with an 100 mg/m^2 etoposide and 60 mg/m^2 cisplatin which resulted in disease stabilization. The preoperative stage was Masaoka IVB. Via a median sternotomy, a 17×12×6.5 cm mass (Fig. 4A) was removed along with the anterior pericardium anterior to both the phrenic nerves 6 weeks later. The mass was hard, reddish, and H-shaped. It was tightly adherent to the superior vena cava, ascending aorta, and pericardium. The pathological examination of the tumor mass (Fig. 4B, C) definitely confirmed an LCNEC of the thymus. The tumor cells showed large nuclei with conspicuous cytoplasm and distinct nucleoli. Neuroendocrine features such as cribriform and trabeculae were observed. Immunohistochemical staining for neuroendocrine markers demonstrated a cytoplasmic staining pattern in the tumor cells. The anterior mediastinal nodes were positive for the tumor cells. The postoperative Masaoka stage was IVB. The patient's postoperative course was uneventful. He was discharged on postoperative day 8. Postoperative radiation therapy was started with 6,000 cGy from the postoperative day 45 at the outpatient department. He is still alive one year after the surgery but metastases were found in the left anterior chest wall and the third lumbar vertebral body.

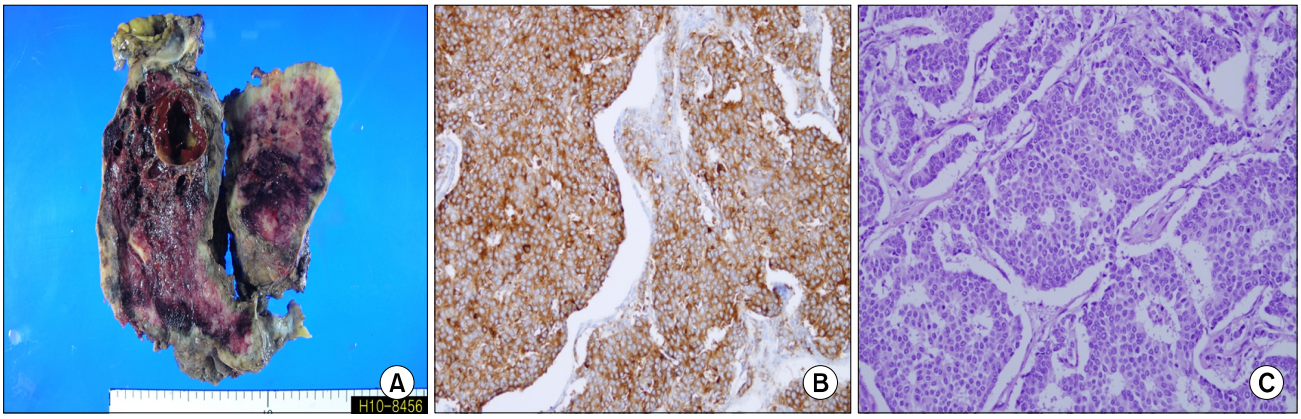

Fig. 4. (A) The gross findings of the anterior mediastinal mass of case 2. The mass shows grayish-tan, fish-flesh, and soft cut surface with multifocal hemorrhagic and cystic areas. (B) The histologic findings of a large cell neuroendocrine carcinoma of case 2. show the tumor cells have large nuclei with conspicuous cytoplasm and distinct nucleoli. Neuroendocrine features such as cribriform, cord, or trabeculae are visible (H&E, ×200). (C) Immunohistochemical staining for the neuroendocrine marker (synaptophysin) demonstrates diffuse cytoplasmic staining pattern in the tumor cells (synaptophysin, ×200).

DISCUSSION

A LCNEC of the thymus is a very rare malignant tumor which has a very poor prognosis. It had been classified as one variation of the carcinoid tumors of the thymus. The concept of LCNEC was first introduced by Travis et al. [1] following an investigation of the spectrum of pulmonary neuroendocrine carcinomas that had been traditionally classified as typical carcinoids, atypical carcinoids, or small cell carcinomas. The authors proposed a fourth category of LCNEC for the higher grade non-small-cell tumors. They had characterized LCNEC by 1) a light microscopic neuroendocrine appearance, 2) large sized, polygonal-shaped cells having a low nuclear-cytoplasmic ratio with coarse nuclear chromatin and frequent nucleoli, 3) a high mitotic rate greater than 10/10 high power fields, and frequent necrosis, and 4) neuroendocrine features by immunohistochemistry or electron microscopy. As such, Moran and Suster [2] have proposed replacing the term thymic carcinoid with thymic neuroendocrine carcinoma and categorized the four types of neuroendocrine carcinoma according to the histological grade and different prognoses. Both typical and atypical carcinoid tumors of the thymus may express neuroendocrine markers such as chromogranin A, synaptophysin, and neuron-specific enolase, but LCNEC and small cell carcinoma of the thymus are weakly or rarely positive for these markers [3]. However, Chaer et al. [4] reported that chromogranin is the most reliable marker of neuroendocrine carcinoma of the thymus. The accurate diagnosis of a thymic tumor by a standard transthoracic needle biopsy is challenging due to the morphologically inhomogeneous character of thymic tumors. A thoracotomy may offer the best chance for a definitive diagnosis and treatment for thymic tumors [5]. We were able to make a final definitive diagnosis of LCNEC of the thymus and confirmed Masaoka stage IVB by thoracotomies in our two cases. There is still no single series or institute of study for these tumors. We were able to find several case reports [3, 5-8] in a Medline search. The detailed clinical features including the long-term prognosis and definitive modalities of treatment for LCNEC of the thymus are still unknown. However, as with other thymic malignancies, we believe that complete resection of LCNEC is the best way to cure the disease. Many reports have shown an extremely poor long-term survival rate (patients usually died within 6 months after surgery) and frequent local recurrence and/or distant metastases after surgical resection of the tumor due to the biologically aggressive behavior of LCNEC [3,5,6]. Cardillo et al. [3] reported that the 10-year survival rate was 100% in typical carcinoid patients but 0% in LCNEC patients. However, Ogawa et al. [7] reported a case of 16 months survival after surgical resection of a

Masaoka stage II LCNEC followed by adjuvant chemotherapy with Cisplatin and Irinotecan. Dutta et al. [8] reported a case of LCNEC with sternal invasion. These two case studies reported a complete en bloc resection with postoperative chemoradiation therapy, which may be beneficial for long-term survival and to prevent local recurrence and distant metastasis [7,8]. To obtain a definite diagnosis and to remove the masses putting pressure on the mediastinum, we had performed radical resection, although incomplete, for our two cases, plus a preoperative chemotherapy procedure in the second case, hoping for a reduction in the tumor size with postoperative chemoradiation. The two patients have been alive for four years and one year to the present day, although they have local recurrences and distant metastases. We believe that the aggressive therapy described in this report may be helpful for improving the quality of life, delaying local recurrence, and increasing survival.

REFERENCES

1. Travis WD, Linnoila RI, Tsokos MG, et al. *Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: an ultrastructural, immunohistochemical, and flow cytometric study of 35 cases.* Am J Surg Pathol 1991;15:529-53.
2. Moran CA, Suster S. *Neuroendocrine carcinomas (carcinoid, atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma): current concepts.* Hematol Oncol Clin North Am 2007;21:395-407.
3. Cardillo G, Treggiari S, Paul MA, et al. *Primary neuroendocrine tumours of the thymus: a clinicopathologic and prognostic study in 19 patients.* Eur J Cardiothorac Surg 2010;37:814-8.
4. Chaer R, Massad MG, Evans A, Snow NJ, Geha AS. *Primary neuroendocrine tumors of the thymus.* Ann Thorac Surg 2002;74:1733-40.
5. Chetty R, Batitang S, Govender D. *Large cell neuroendocrine carcinoma of the thymus.* Histopathology 1997;31:274-6.
6. Tiffet O, Nicholson AG, Ladas G, Sheppard MN, Goldstraw P. *A clinicopathologic study of 12 neuroendocrine tumors arising in the thymus.* Chest 2003;124:141-6.
7. Ogawa F, Iyoda A, Amano H, et al. *Thymic large cell neuroendocrine carcinoma: report of a resected case - a case report.* J Cardiothorac Surg 2010;5:115.
8. Dutta R, Kumar A, Jindal T, Mathur SR. *Neuroendocrine carcinoma of the thymus gland with sternal invasion.* Interact Cardiovasc Thorac Surg 2009;8:694-6.