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Case Report
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Thymic Large-Cell Neuroendocrine Carcinoma: A Case Report and Review of a Japanese Case Series

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Abstract

Large-Cell Neuroendocrine Carcinoma (LCNEC) of the thymus is a rare, aggressive cancer that leads to a poorer prognosis than other thymic epithelial tumors. A 54 year old Chinese male presented with an anterior Mediastinal mass as per chest computed tomography findings. Histological examination after thymothymectomy revealed primary thymic LCNEC. We reviewed 40 cases of this rare cancer that have been reported in Japan. To our knowledge, even though thymic LCNEC is sub classified as part of the thymic NEC group in accordance with the classification of pulmonary neuroendocrine tumors, the detailed clinical features and therapeutic management remain unknown.

Keywords: Large-cell neuroendocrine carcinoma; Thymic cancer; Prognosis

Introduction

Large-Cell Neuroendocrine Carcinoma (LCNEC) of the thymus is a rare malignant tumor that is more aggressive and leads to a poorer prognosis than other thymic epithelial tumors. Herein we describe a rare case of LCNEC of the thymus and review 40 cases of this disease that have been reported in Japan.

Case Report

A 54-year-old Chinese man was admitted to the St. Marianna University School of Medicine Hospital in October 2017 for further examination and treatment following the identification of an abnormal shadow in chest X-ray during a regular health checkup. The patient's medical history included right renal infarction controlled by aspirin and hypertension treated with amlodipine and current smoking with 1.25 pack-year. The chest X-ray showed a solid mass with a clear border at the left hilum and an appearance of paravertebral body line (Figure1A). Enhanced chest Computed

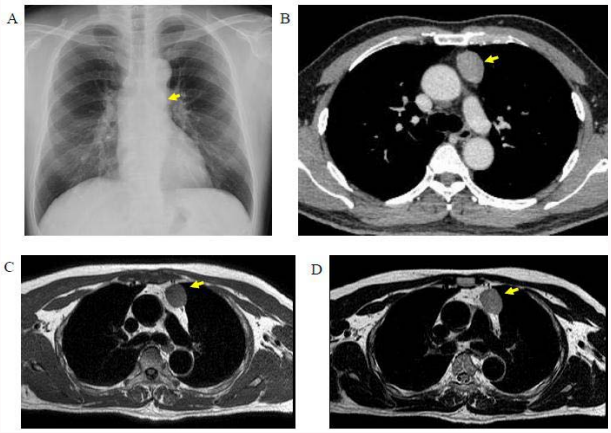

Figure 1: Preoperative Chest X-ray and CT findings showed a solid mass with a clear border in the anterior mediastinum (arrow) (A, B). Chest MRI showed that the tumor had signal characteristics similar to the muscle on T1-weighted images. On T2-weighted images, the signal was higher than the muscle and revealed homogeneous enhancement (C, D).

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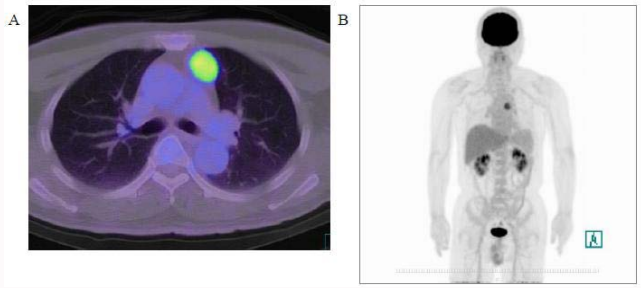

Figure 2: FDG-PET images reveal an anterior Mediastinal tumor with high FDG accumulation with a standardized uptake value max (SUV max) of 9.9, with no other abnormal FDG uptake, including the testes (A, B).

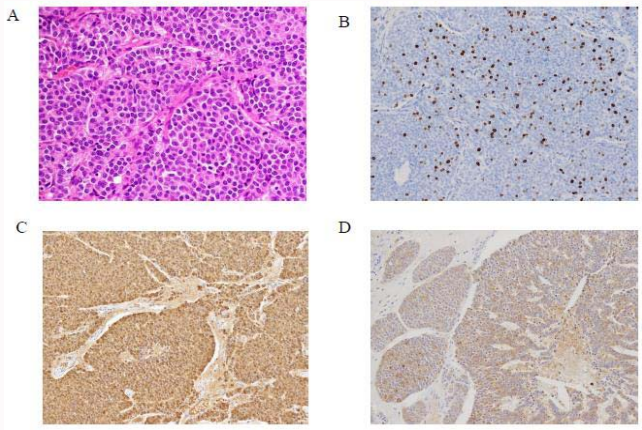

Figure 3: Microscopy findings showed that the tumor cells were round-to-oval shaped with small foci of coagulation necrosis (A). Mitotic counts were >10 cells/10 HPF, and the Ki-67 indices using MIB-1 immuno-histochemical staining ranged from 10% to 20% (B). Immuno-histochemical findings showed that the tumor cells strongly expressed synaptophysin (C) and chromogranin A (D).

Tomography (CT) findings revealed a large, homogeneous, solid mass (3.5 cm) occupying the anterior mediastinum (Figure 1B). Magnetic Resonance Imaging (MRI) findings revealed that the tumor shared similar signal characteristics with the muscle on T1-weighted images. On T2-weighted images, the signal intensity was higher than that for muscle and revealed homogeneous enhancement. No signs of invasion of the aorta and pulmonary artery or metastases to other organs (Figure 1C and 1D) were noted. Fluoro-2-deoxyglucose positron emission tomography–computed tomography (FDG-PET/CT) findings revealed the presence of an anterior Mediastinal tumor with high FDG accumulation with a standardized uptake value max (SUV max) of 5.3 (Figure 2A and 2B). Laboratory findings and results for tumor markers including CEA, CA125, CA19-9, SCC antigen, NSE, CYFRA, Pro-GRP, Alpha-fetoprotein, and IL-2 receptor were all within normal ranges preoperatively. Following the radiological diagnosis of thymoma, the patient underwent an extended thymothymectomy. Post median sternotomy, the thymus had macroscopically invaded the surrounding fatty tissue and adhered to the left pleura and the great vessels. Microscopically, the tumor had the morphologic features of a neuroendocrine tumor. The tumor cells were round-to-oval shaped and small foci of coagulation necrosis were observed (Figure 3A). Capsule invasion was also noted, but no invasive cancer cells existed in the connective tissue outside the capsule. Mitotic counts were >10 cells/10 HPF and the Ki-67 indices using MIB-1 immuno-histochemical staining ranged from

Table 1: Summary of 40 thymic N (%) LCNECs reported between 1999 and 2017 (Japan).

Variables		N (%)
Gender	Male	17 (42%)
	Female	21 (53%)
	Unknown	2 (5%)
Age	<50	10
(Median age = 57 [30–75])	50–60<	11
	60–70<	14
	70–80<	2
	Unknown	3
Tumor size (mm)	<50 mm	10
(Average size = 52.6 [13-100])	50 mm-100 mm	14
	≥ 100 mm	1
	Unknown	15
Masaoka stage	I	6
	II	6
	III	8
	IVa	3
	IVb	11
	Unknown	6
Treatment	Ope	35
	Ope + Cx + RT	14
	Ope + Cx	9
	Ope + RT	3
	Only Ope	9
	Only Cx	2
	Cx + RT	1
Prognosis	Unknown	2
	Recurrence	15 (Alive: 7 / Dead: 4 / Unknown: 4)
	No recurrence	13
	Unknown	12

10% to 20% (Figure 2B). Immuno histochemistry findings revealed that the tumor cells strongly expressed Cytokeratin (CK) AE1/AE3, synaptophysin (Figure 2C), and CD56. Tumor cells were negative for CD5, CD20, P40, EMA, and p63 and were partially positive for chromogranin A (Figure 3D). The patient was finally pathologically diagnosed with LCNEC of the thymus, which was classified as a stage I tumor on the basis of Masaoka classification. The patient was treated using four courses of adjuvant chemotherapy on the basis of a platinum doublet using a cisplatin (80 mg/m^2) and etoposide (100 mg/m^2) regimen. No recurrence was detected six months post-treatment.

Discussion

Thymic NECs are relatively rare neoplasms that account for 2% to 4% of all anterior Mediastinal neoplasms [1]. Primary thymic LCNEC is a high-grade malignant thymic tumor that comprises large cells with neuroendocrine morphology and either neurosecretory granules as observed on electron microscopy or positive neuroendocrine immuno-histochemical markers [2]. Even though LCNEC is sub classified as part of the thymic NEC group in accordance with the classification of pulmonary neuroendocrine tumors, the detailed

clinical features of LCNEDC remain unknown. Fourty cases, including the present case, of primary thymic LCNEC have been reported until 2017 in the Japanese literature (Table 1). The average age of patients was 53.7 years (range 30-75 years). Patients included 17 men, 21 women, and 2 patients with an unshared gender. In general, thymic neuroendocrine tumors (NETs) occurred in patients who were approximately 50 years of age [3]. Thymic LCNEC is a high-grade malignant tumor composed of large cells with neuroendocrine features. The high-grade tumors (SCNEC and LCNEC) are less common in men compared with the carcinoid tumor. Therefore, the present case can be considered as relatively rare.

The symptoms of thymic cancer may be associated with the tumor itself or be part of a condition related to the cancer. However, they are not directly caused by the tumor mass. Examples of symptoms include shortness of breath, cough, chest pain, and swelling of the face. Some patients with thymic LCNEC do not show any symptoms and are identified by an abnormal shadow on the chest X-ray during a regular checkup. Regardless of the presence of symptoms, thymic LCNEC is more aggressive than other thymic epithelial tumors and LCNECs present primarily during advanced clinical stages. At this stage, patients already have an advanced disease stage or metastatic tumors. Detailed clinical features, long-term prognosis, and definitive modalities of treatment for LCNEC of the thymus remain unknown. Studies have reported that the clinical behavior and prognosis of lung LCNEC are similar to Small Cell Lung Cancer (SCLC). SCLC-based regimens are considered to be effective in patients with LCNEC. Therefore, postoperative adjuvant chemotherapy consisting CDDP and VP-16 is recommended, which is the treatment protocol for SCLC. We believe that the regimen may be effective in cases of thymic LCNEC, which has a poorer prognosis than other neuroendocrine tumors because of the frequent distant and lymph node metastases. Four cancer-related deaths occurred during follow-up, 14 patients had recurrence including metastases. The median survival time was 14 months in our Japanese series. Shoji et al. reviewed 13 cases of thymic LCNECs worldwide [4]. The five-year overall survival and five-year disease-free survival rates were 66% and 43%, respectively. In the present case, the potential risk of recurrence necessitates regular follow-up.

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References

1. Chetty R, Batitang S, Govender D. Large cell neuroendocrine carcinoma of the thymus. Histopathology. 1997;31(3):274-6.
2. Moran CA, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases. Am J Clin Pathol. 2000;114(1):100-10.
3. Ogawa F, Amano H, Iyoda A, Satoh Y. Thymic neuroblastoma with the syndrome of inappropriate secretion of antidiuretic hormone. Interact Cardiovasc Thorac Surg. 2009;9(5):903-5.
4. Shoji T, Fushimi H, Takeda S, Tanio Y. Thymic large-cell neuroendocrine carcinoma: a disease neglected in the ESMO guideline? Ann Oncol. 2011;22(11):2535.