Gen Thorac Cardiovasc Surg (2008) 56:566–569
DOI 10.1007/s11748-008-0299-7

CASE REPORT

Large-cell neuroendocrine carcinoma in the thymus

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Received: 8 April 2008 / Accepted: 3 July 2008

Abstract Large-cell neuroendocrine carcinoma in the thymus is a rare cancer that is more aggressive and leads to a poorer prognosis than other thymic epithelial tumors. A 67-year-old woman presented with an anterior mediastinal mass in the thymus. Histological examination after thymectomy revealed large-cell neuroendocrine carcinoma in the thymus. Although the patient received postoperative chemotherapy and radiotherapy, a distant relapse was detected 6 months after the surgery. We reviewed nine cases of this rare cancer that have been reported in Japan. There is no evidence of to support postoperative therapy for large-cell neuroendocrine carcinoma in the thymus. However, it is essential to accumulate and study these cases to understand this disease and prolong patient survival.

Key words Large-cell neuroendocrine carcinoma · Thymic carcinoma · Thymus

Introduction

Large-cell neuroendocrine carcinoma (LCNEC) in the thymus is a rare cancer that is more aggressive and leads to a poorer prognosis than other thymic epithelial tumors. We describe here a rare case of LCNEC in the thymus and review nine other cases of this disease that have been reported in Japan.

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Case

A 67-year-old woman was admitted to our hospital in November 2006 with an anterior mediastinal mass that was detected on a chest computed tomography (CT) scan. She had received follow-up care for several years at another hospital because of hypertension. She had smoked 10 cigarettes a day for 47 years.

Blood tests showed that the levels of lactate dehydrogenase (LDH) 421 IU/l/37°C, nonspecific enolase (NSE) 12.0 ng/ml, and Type 1 collagen C-terminal telopeptide (ICTP) 6.4 ng/ml were high. The levels of carcinoembryonic antigen (CEA), squamous cell carcinoma-related antigen (SCC), pro-gastrin-releasing peptide (Pro-GRP), adrenocorticotropin hormone (ACTH), antidiuretic hormone (ADH), cortisol, and anti-acetylcholine (anti-ACh) receptor antibody were normal.

The patient was in good general condition, and she did not have any neurological or endocrine disorders. We did not observe any typical symptoms of thymic tumors such as myasthenia gravis. CT and magnetic resonance imaging (MRI) revealed a large, heterogeneous, solid mass (5 cm) occupying the anterior mediastinum (Fig. 1). There were no signs of metastases to other organs. The patient received an initial diagnosis of a Masaoka stage II thymoma,[1] and an operation was performed.

A median sternotomy revealed that the thymus had macroscopically invaded the surrounding fatty tissue and adhered to the left pleura and the great vessels

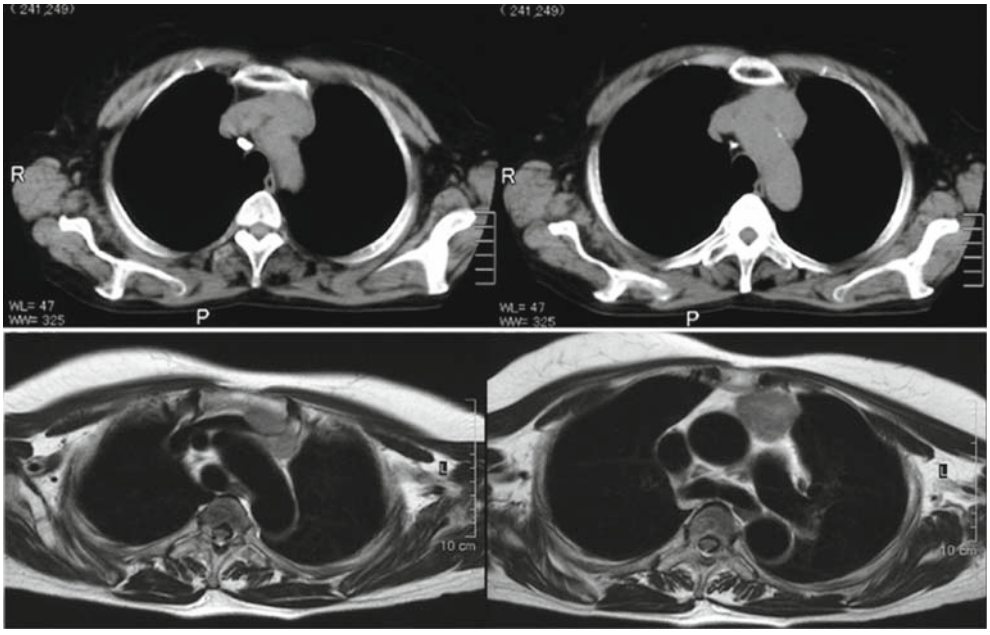

Fig. 1 Preoperative computed tomography showed a mass in the anterior mediastinum (*top*), and magnetic resonance imaging (MRI) revealed the mass (*bottom*). This mass adhered to the pleura and extended above the left innominate vein

without invasion. Pulmonary metastases were not observed, but the supraclavicar lymph nodes were swollen; thus, these lymph nodes were resected, and total thymectomy was performed with the tumor being completely resected.

The resected tumor was an elastic, hard, tan-brown, infiltrative mass that measured 5.0×6.0 cm. Microscopically, the tumor consisted of large pleomorphic cells with a high nuclear-to-cytoplasmic ratio. The tumor cells displayed prominent neuroendocrine architectural features, such as a trabecular pattern and rosetting with necrotic interstitium (Fig. 2A). Mitotic counts were in excess of 10 cells per 10 HPF (Fig. 2B). Metastases were observed in the resected supraclavicular lymph nodes (Fig. 2C). These carcinoma cells were strongly immunopositive for neural cell adhesion molecule (NCAM)/CD56 (Fig. 2D), but lacked chromogranin and synaptophysin. The tumor fulfilled the criteria for a diagnosis of LCNEC of the thymus[2] and was classified as a stage IVb tumor based on Masaoka's classification.

The patient's postoperative course was good, and she was discharged 10 days after the operation. Four weeks after the operation, she was readmitted to the hospital to receive adjuvant chemotherapy consisting of CDDP at 80 mg/m^2 and VP-16 at 100 mg/m^2 with two cycles and radiotherapy (a total dose of 65 Gy) from the mediastinum to the left cervical area.

After the postoperative therapy, the patient was monitored with regular follow-up visits. Six months after the operation, a recurrence was indicated by the appearance of brain metastasis. Later, multiple bone metastases appeared. The patient received supportive care for her symptoms and died 9 months after the operation due to multiple metastases.

Discussion

Primary thymic neuroendocrine carcinomas (NECs) are relatively rare neoplasms that may account for approximately 2%–4% of all anterior mediastinal neoplasms.[3] In 1999, the World Health Organization (WHO) thymic epithelial tumor criteria reclassified thymic carcinoma as type C and referred to NECs as a subtype.[4] The neuroendocrine subtype of the thymus was defined on the basis of histopathological features and immune phenotypes. In a recent study,[5,6] NECs were morphologically categorized into four main types: typical carcinoid, atypical carcinoid, LCNEC, and small-cell carcinoma. LCNECs and small-cell carcinomas are more highly malignant and have a poorer prognosis than other thymic epithelial tumors. LCNEC is included as a separate entity because of differences from carcinoids in survival rates, as well as its incidence and clinical, epidemiologic, histological, and molecular characteristics.

For optimal treatment, an accurate pretherapeutic diagnosis is important. However, as a thymic tumor is not always morphologically homogeneous, accurate pretherapeutic diagnosis by a standard needle biopsy is difficult.[7] Surgery offers the best chance for a definitive diagnosis and curative treatment for thymic tumors. To make a successful differential diagnosis, the application of detailed immunohistochemical analyses, such as NCAM/CD56, may be useful for NECs.

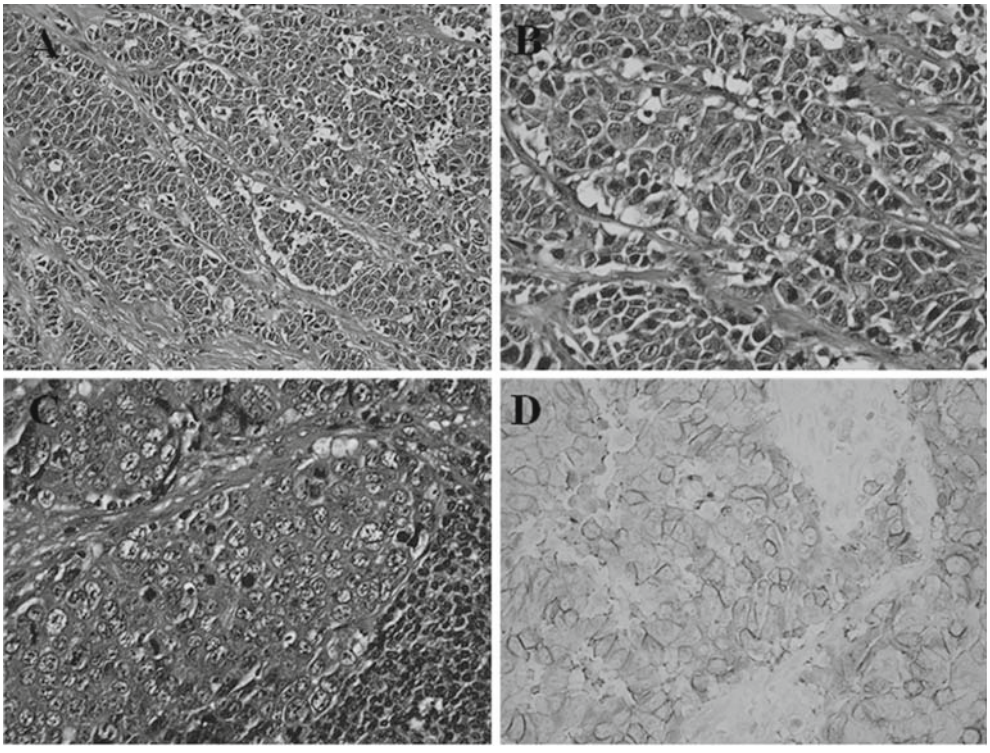

Fig. 2 **A** Large pleomorphic cells displaying prominent neuroendocrine architectural features, such as a trabecular pattern and resetting. (H&E, ×100) **B** Large pleomorphic cells with cytologic atypia, large nuclei, a coarse chromatin network, a high nuclear/cytoplasmic ratio, and frequent nucleoli. Mitotic counts were in excess of 10 cells per 10 high power fields. (H&E, ×400) **C** Tumor cell metastases were observed in the resected supraclavicular lymph node. (H&E, ×400) **D** Large tumor cells showed strongly immunopositive staining for NCAM/CD56. (×400)

There have been 10 reports (including our case) about LCNEC of the thymus in Japan, but only one article has been published (Table 1).[7] These 10 cases consist of 2 men and 7 women (one report did not give the sex of the patient); thus, LCNEC tends to be observed mainly in women. The average age of the male patients was 48.0 years (range 46–50 years), and the average age of the female patients was 62.7 years (range 53–69 years). Surgery was performed in 8 of the 10 cases. A relatively large number of the tumors were advanced-stage disease. Almost all patients developed recurrences within a short amount of time (e.g., 2 months after the operation), but different postoperative therapies were performed at each hospital. The recurrences were similar to that in our case, and they ranged from supraclavicular lymph node metastasis to multiple bone or organ metastases. These recurrences are caused by the malignant potential of LCNEC and the anatomical characteristics of the thymus in relation to the left innominate vein or lymph duct.

Patients with LCNEC in the thymus have a poor prognosis. Some reports indicate that complete surgical excision and adjuvant therapy seems to be curative and is a significant factor for prolonged survival.[8,9] Currently, there is no evidence of to support the use of postoperative therapy. A recent study of LCNEC in the lung recommended postoperative administration of adjuvant chemotherapy consisting of CDDP and VP-16, which is the treatment protocol for small-cell lung carcinoma. Likewise, we selected this postoperative therapy for our patient. We believe that surgery and adjuvant therapy are needed to treat LCNEC in the thymus. The adjuvant therapy may be effective at an earlier stage.

Our patient was successfully treated with a complete resection that led to an accurate diagnosis and postoperative chemotherapy and radiotherapy. Although she did not have microscopic residual disease after the operation, a distant relapse occurred 6 months after the surgery. Previous reports have shown the high rate of distant relapse of LCNEC in the thymus and have suggested that adjuvant chemotherapy be considered.[8,9] However, the modalities for adjuvant chemotherapy remain to be defined.

Table 1 LCNEC of the thymus documented in Japan

Case no.	Age/sex	Study (year)	Size (mm)	Masaoka stage	Treatment	Prognosis
1	53 F	Kurashima (2002)	50	IVa	Op+Cx+Rx	*
2	50 M	Miura (2003)	40	IVa	Op	*
3	63 F	Hirami (2004)	50	IVb	Op+Rx	4 M recurrence
4	57 F	Nagata (2005)	70	II	Op+Rx	7 M recurrence
5	69 F	Kitagawa (2006)	70	IVb	Cx	*
6	*	Shimokawa (2006)	*	*	*	*
7	46 M	Tao (2006)	*	IVb	Op	4 M recurrence
8	63 F	Tao (2006)	*	IVb	Op+Cx+Rx	4 M recurrence
9	67 F	Kou (2007)	*	IVa	Op+Cx+Rx	*
10	67 F	Our case	60	IVb	Op+Cx+Rx	6 M recurrence

LCNEC, large-cell neuroendocrine carcinoma in the thymus; *, no description; Op, operation; Cx, chemotherapy; Rx, irradiation; M, postoperative month

Conclusion

Because LCNEC in the thymus is rare, it is necessary to document and study cases of this disease to understand its pathology and prolong patient survival. More case reports are needed to clarify the biological behavior and determine the suitable treatment for this rare neoplasm.

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