

Mucoepidermoid Carcinoma of the Thymus Treated by Multimodality Therapy: A Case Report

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A case report of mucoepidermoid carcinoma of the thymus, aggressively treated by multimodality therapy including surgery, radiotherapy, chemothermotherapy, and systemic chemotherapy is presented. The patient, a 53-year-old man, underwent potentially complete resection for an anterior mediastinal tumor, histologically diagnosed as a mucoepidermoid carcinoma of the thymus with Masaoka stage II disease. However, because of local recurrences in the left chest wall and pleura, re-resection was twice performed 4 years and 5 months, and 5 years and 7 months after the initial surgery, in combination with intrathoracic chemothermotherapy and irradiation. Seven years and 1 month after the initial operation, in vitro chemosensitive test based-chemotherapy using vinorelbine for pleural disease was performed, resulting in maintenance of good quality of life (QOL) due to dramatic decrease in pleural effusion. He died of tumor progression, 7 years and 9 months after the initial treatment. Although the clinical aspects of thymic mucoepidermoid carcinoma are little known, it is assumed that such aggressive therapeutic multimodalities as repeated surgical resection, irradiation and chemothermotherapy, and chemotherapy based on in vitro chemosensitivity tests contributed to long-term survival for this unusual disease. (Ann Thorac Cardiovasc Surg 2006; 12: 273–8)

Key words: thymus, mucoepidermoid carcinoma, surgery, collagen gel droplet drug sensitivity test

Introduction

Mucoepidermoid carcinoma is a malignant neoplasm mainly originating in the salivary glands or the bronchus,^{1–3)} mucoepidermoid carcinoma is extremely rare, accounting for only 1.7% of thymic carcinomas.⁴⁾ To date, thymic mucoepidermoid carcinoma has been reported by only a few researchers around the world.^{4–11)} The clinical aspects and therapeutic modalities of this disease remain unknown.

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We recently experienced a case which was aggressively treated by multimodality therapy including repeated surgery, radiotherapy, chemothermotherapy, and systemic chemotherapy with long-term survival. This rare case is presented, focusing on the clinical course and therapeutic multimodality for this disease.

Case Report

In May 1996, a 53-year-old man was admitted to our institute with an asymptomatic hilar mass in the left thoracic cavity. He had no specific family history or past history. He had smoked 20 cigarettes per day for 32 years. The serum levels of tumor markers such as carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC) antigen, and cytokeratin-19 fragments (CYFRA) were all within the normal range. Although a plain chest radiogram revealed a 5 cm-sized mass at the hilum in the left pleural cavity, computed tomography (CT) revealed



Fig. 1. Chest-enhanced computed tomography (CT) of the patient before radical resection.

A well-defined anterior mediastinal mass was shown within the thymus area in contact with the ascending aorta to the left main pulmonary artery, but without definite findings of invasion to the neighboring organs (arrow). A patchy calcified shadow and low-density area were partially observed within the mass.

a well-defined anterior mediastinal mass in contact with the ascending aorta along to the left main pulmonary artery, but without definite findings of invasion to the neighboring organs (Fig. 1). A patchy calcified shadow was partially observed within the mass. A chest magnetic resonance imaging (MRI) scan revealed a mass of homogenous low intensity in the T1-weighted images, which was heterogenous on T2-weighted images. Following intravenous injection of the contrast agent on MRI, the mass was enhanced with partially cystic formation. This was suspected to be a mediastinal tumor and he underwent a left thoracotomy on June 8, 1996. Intraoperatively the mass was diagnosed as a mucoepidermoid carcinoma of the thymus, and an extended thymus resection and regional lymph node dissection was performed. The patient's postoperative course was uneventful.

The resected tumor measured 5.5×4.0 cm in size and was a solid mass with calcification and cystic parts (Fig. 2). Histologically, the tumor shared a biphasic appearance characterized by a mixture of the solid proliferation of squamous cell elements with low grade cytologic atypia and duct-forming proliferation of mucus-producing cell elements (Fig. 3). Mitosis was rare. Periodic acid-Schiff (PAS) staining revealed abundant mucin in the cytoplasm of tumor cells forming the acini. Thus, histological findings were compatible with well-differentiated mucoepidermoid carcinoma. Tumor cells microscopically invaded into the capsule, but were not exposed through

the mediastinal pleura. Neither vascular nor nodal involvement was observed. The tumor, although having a low grade of malignancy, was classified as a type C thymic tumor of the World Health Organization (WHO) classification¹²⁾ and was in pathological stage II according to the staging system of Masaoka.¹³⁾ Thus, the present tumor was judged to be potentially completely resectable.

Four years and 5 months after the initial operation, however, a left parasternal chest wall mass, 2 cm in size, was detected in a routine follow-up chest CT. This was completely resected on March 30, 2001, and judged as local recurrence in the pleura invading into the chest wall. A year later (5 years and 7 months after the first operation), several localized disseminated tumors, 3.5 cm or less in size were detected, again in the neighborhood of the second resected site. These tumors were widely removed in a combined partial resection with the anterior chest wall, sternum and lung on March 28, 2002. Postoperative intrathoracic chemothermotherapy (PICT) using carboplatin¹⁴⁾ and irradiation of 60 Gy were given as adjuvant therapy against the microscopically residual disseminated lesions.

For about a year after these multimodality therapies, the patient was clinically disease-free and maintained a good quality of life (QOL, PS 0). Seven years and 1 month after the first operation, a tumor relapse occurred with an elevated serum CEA level and pleural effusion. According to the data of an in vitro chemosensitive test, a col-



Fig. 2. Cut surface of the resected mass specimens after formalin fixation.

In the resected specimen, the tumor measured 5.5×4.0 cm and showed a separate solid growth pattern, including calcification and cystic parts.

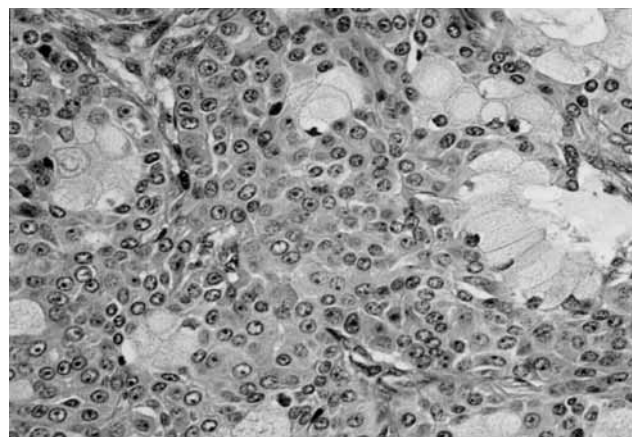


Fig. 3. Photomicrography of the tumor.

The tumor had a biphasic appearance characterized by an admixture of the solid proliferation of squamous cell elements with low grade cytologic atypia and duct-forming proliferation of mucus-producing cell elements. These findings were histologically compatible with those of mucoepidermoid carcinoma, a well-differentiated type. (HE stain: ×400)

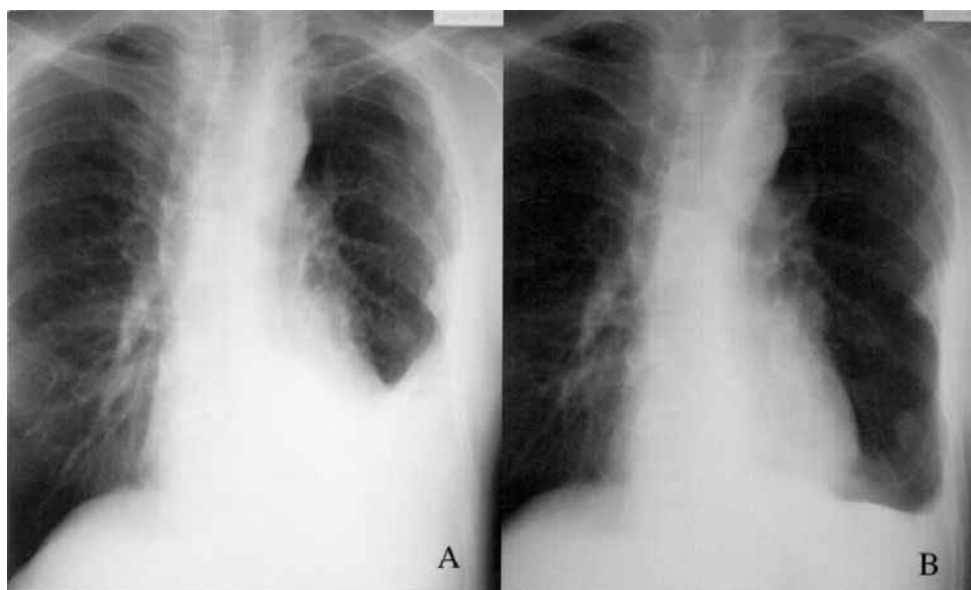


Fig. 4. Chest radiographs before (A) and after (B) systemic chemotherapy using vinorelbine for recurrent disease in the pleural cavity. Systemic chemotherapy using vinorelbine for recurrent disease in the pleural cavity was performed in July 2003. Despite stable disease in the disseminated mass, pleural effusion was dramatically decreased, resulting in quality of life (QOL) improvement for more than 2 months.

lagen gel droplet drug sensitivity test (CD-DST)¹⁵⁾ using the third set of resected materials, systemic chemotherapy using vinorelbine (30 mg/m²×4 courses) was performed in July 2003. Serum CEA levels and pleural effusion dramatically decreased, resulting in improvement of QOL for more than 2 months (Fig. 4). Finally, on March 25, 2004, 7 years and 9 months after the initial treatment, the patient died of tumor progression. At autopsy, the tumor had recurred not only into the left pleural cavity, but also

into the abdominal cavity and liver.

Comment

Thymic carcinoma is a rare neoplasm of the thymus, and unlike a thymoma, it exhibits malignant features of obvious cytologic atypia, having a more aggressive propensity for early local invasion and wide spread metastases. It includes the following subtypes: SCC, lym-

phoepithelioma-like carcinoma, neuroendocrine carcinoma, adenosquamous cell carcinoma, clear cell carcinoma, papillary carcinoma, basaloid carcinoma, sarcomatoid carcinoma, and mucoepidermoid carcinoma.^{12,16)} The most common histologic type is SCC, usually occurring in middle-aged men.^{4,7)} The prognosis of thymic carcinoma is poor because of early metastatic involvement of the pleura, lungs, lymph nodes of the mediastinum, bone and liver.¹⁷⁻¹⁹⁾ Local recurrences and distant metastases are frequent, occurring at 35% and 50%, respectively.^{4,7)} The overall survival rate at 5 years for thymic carcinoma is reported to be approximately 35%.^{4,7)} Importantly, the histologic type constitutes the most reliable and important predictor of prognosis.^{4,16,17)} In fact, thymic carcinomas have been roughly classified as either low- or high-grade malignancy.⁴⁾ The low-grade tumors with relatively favorable prognoses include SCC, mucoepidermoid carcinoma and basaloid carcinoma, whereas the high-grade tumors include the others with poor prognosis.

Although it appears that mucoepidermoid carcinoma of the thymus is extremely rare, its histological characteristics have been well analyzed: It is composed of variably-sized cysts, lobules, sheets and nests of such tumor cells as epidermoid cells, mucus-secreting cells, and occasionally intermediate type cells in a variable admixture.^{8,11)} The epidermoid cells show various grades of keratinization. Mucus-secreting cells, resembling goblet cells, are usually polygonal with copious intracellular mucin, and form small nests, line cyst walls, and are often interspersed as single or small clusters between the epidermoid cells. The third cells, composed of polygonal cells with a nondescript appearance, are usually intermingled with the other types. The tumor stroma is generally fibrotic, and hyalinized occasionally with focal calcification. These histological features are similar to those arising from the salivary glands and other areas.¹⁻³⁾ Also, gross findings of this tumor are characterized by a combination of solid and cystic areas in various proportions. The former show as a lobulated or firm mass, whereas the latter contain mucoid materials occasionally with multilocular cystic structures. In the present case, such histological and gross features were well observed, and this tumor was finally diagnosed as mucoepidermoid carcinoma of the thymus. To our knowledge, there are only 4 cases previously reported in Japan, and the present case was the 5th.^{5,20-22)}

As described above, thymic mucoepidermoid carcinoma is generally considered to be a low-grade malig-

nancy with a good prognosis.⁴⁾ However, Moran et al.⁸⁾ emphasized that histological differentiation of this tumor was an important characteristic reflecting its clinical behaviour: The well-differentiated type, in which mitosis was virtually absent, was not fatal, while the poorly differentiated type was clinically aggressive enough to threaten life, and cellular atypia, mitosis, necrosis, and predominance of an epidermoid component were often observed. A similar histological classification is commonly observed arising from the head and neck area, showing a good correlation between tumor differentiation and prognosis.²⁾ Although the present primary tumor was regarded as the well-differentiated type because of the slight mitosis, necrosis and cellular atypia. It recurred as long as 4 years and 5 months after the initial resection, ultimately with an unfavorable clinical outcome. Considering the findings of neither lymphatic nor vessel invasion in the primary tumor and the repeated local recurrence in the pleural cavity, it can be speculated that the primary tumor might have invaded into the mediastinal pleura, although this pleural involvement could not be directly demonstrated. Thus, even if the tumor is a well-differentiated type, when capsular invasion is positive, that is, the tumor is stage II or more advanced on Masaoka's staging system,¹³⁾ local recurrence, especially pleural dissemination, may be mostly guarded, as with other types of thymic carcinoma in addition to invasive thymoma. In fact, reviewing the previous reports regarding completely resected low-grade mucoepidermoid carcinoma of the thymus, only case 1 (stage III disease at surgery) reported by Nonaka et al.¹¹⁾ died of disease with local recurrence. On the other hand, all the patients with histologically high-grade mucoepidermoid carcinomas of the thymus showed poor outcomes with tumor extremely aggressive progression.^{8,11)} For example, according to the report by Nonaka et al.,¹¹⁾ even a patient with the high-grade type, but with stage I disease (case 9) died. Thus, accurate histologic subtyping, namely tumor differentiation as well as clinical staging are highly recommended for the diagnosis and treatment of this disease. Especially, when the tumor is anatomically located in contact with the pleura cavity, more accurate and careful staging may be clinically necessary in the long-term follow-up.

If complete resection is possible, this type of tumor should be removed by surgery, as with other types of thymic carcinoma. Takahashi et al.²³⁾ reported that in a limited early stage of thymic carcinoma, surgical resection was adequate for treatment, although the rate of complete resection is only 20-35%.^{7,18,24)} However, if the tumor is

advanced or recurrent, a multimodality approach, including surgical resection, radiation, chemotherapy, or a combination selected.^{24,25)} In the present case, chest wall resection was performed twice for local dissemination in the pleural cavity. We believe that these aggressively repeated surgeries contributed to chest pain control and an improvement in the general condition in combination with radiotherapy. In addition, PICT might be also promising for local control, as previously reported by Higashiyama et al.²⁶⁾ for invasive thymoma, as well as by Kodama et al.¹⁴⁾ for lung cancer. Thus, such local therapies should be aggressively performed if the disease is confined within the chest.

On the other hand, systemic chemotherapy with cisplatin-based regimens similar to those of thymoma, has produced various responses in a small number of thymic carcinoma patients.^{24,27,28)} Representatively, ADOC (cisplatin, doxorubicin, vincristine and cyclophosphamide) chemotherapy for advanced thymic carcinoma showed a high clinical response of 75%,²⁸⁾ and in addition, neoadjuvant chemotherapy for this disease with locally advanced stage has been reported in a small number of patients.²⁵⁾ Unfortunately, these modalities have been proposed for thymic carcinoma, and are not specific to mucoepidermoid carcinoma. No available non-surgical, chemotherapeutic, modalities have been reported for patients with advanced stage thymic mucoepidermoid carcinoma. Although several promising chemotherapy regimens have been proposed for patients with malignant head and neck tumors,^{2,29,30)} few have been described for mucoepidermoid carcinoma arising from the head and neck area.²⁾ To overcome the outcome of poor data on chemosensitivity in this rare disease, we applied CD-DST data to practical chemotherapy.³¹⁾ In our institute, CD-DST has been successively performed for lung cancer patients, and it was shown that CD-DST using surgically resected materials might be a promising candidate for screening of potentially effective chemoagents.¹⁵⁾ The present tested specimens were easily obtained by repeated surgery, and as a result, chemotherapy using vinorelbine, predicted to be in vitro-sensitive by CD-DST, was clinically effective for temporary control of pleural effusion with an improvement in the QOL. We believe that under the current situation with no available chemotherapy regimen for such rare diseases, CD-DST might provide potentially promising information for selecting effective chemoagents. Also, considering the data of vinorelbine-chemotherapy for salivary gland malignancies by Airoidi et al.,²⁹⁾ more clinical studies may be necessary to esti-

mate the benefit of chemotherapy using this vinorelbine-based regimen alone.

In conclusion, we herein described a rare case of thymic mucoepidermoid carcinoma undergoing multimodality treatment, including repeated surgical resection, irradiation and chemothermotherapy, and chemotherapy based on an in vitro chemosensitivity test. Although clinical aspects of this disease are little known, it was assumed that such aggressive therapy contributed to long-term survival, while successfully maintaining the patient in good condition. Further clinical analysis is necessary by accumulating data on this unusual disease.

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