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Concurrence of Recurrent Thymoma and Lung Cancer
A Case Report and Review of Literature

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A 46-year-old female was found to have concurrence of recurrent thymoma and lung cancer because of a transient blephaloptosis which appeared 14 years following removal of the primary thymoma. Primary thymoma was non-invasive, but recurrent thymoma invaded anterior chest wall. One year after the second operation, blephaloptosis recurred and the patient was diagnosed as myasthenia, occular type. Recurrence of non-invasive thymoma is rare. And that recurrent thymoma occurred simultaneously with lung cancer is not found in the literature. Occurrence of extra-thymic malignancy has no relationship with the progression of thymoma and may present in multiple organs. Elevation of serum-CEA was noted in the present case. Review of the thymomas treated in our department shows that serum-CEA may be used as an indicator of recurrence or progression of thymoma.

Recurrence is frequently seen in invasive thymoma, but rare in totally resected non-invasive thymoma. A variety of non-thymic malignancies have been reported in association with thymoma. Very little information is available for the concurrence of a recurrent non-invasive thymoma with a lung cancer. In this report, the literature was reviewed and analyzed to search the causes of recurrence of non-invasive thymoma, and the relationship between thymoma and non-thymic malignancy.

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CASE REPORT

Patient was a 46-year-old female. On a routine examination at age 32, chest x-ray showed a right hilar mass shadow. At that time, an encapsulated anterior mediastinal tumor was resected without difficulty through a median sternotomy. The pathologic diagnosis was benign (or non-invasive), lymphocytic type of thymoma. There was no complication of parathymic syndrome in her history.

Acute onset of left blephaloptosis occurred 14 years after removal of the thymoma. Chest x-ray demonstrated a large mass shadow in the right cardiophrenic angle and a small mass shadow in the right mid-lung field. Recurrence of the thymoma with pulmonary metastasis was suspected and she was admitted for further examination. The symptom of blephaloptosis disappeared without medical treatment on admission.

On physical examination, a 2.5×2.0 cm, ill-defined elastic and hard tumor was palpated at the medial side of the right hypochondrium. No lymphadenopathy was observed in the neck and the bilateral axillae. CT scan at the level of the xiphoid process showed a regular homogenous mass protruding from the anterior lower mediastinum to the right thoracic cavity and involving the right anterior chest wall. CT scan at the level of the carina demonstrated an irregular mass in the superior segment of the right lower lobe with pleural indentation. No enlargement of mediastinal lymph nodes was found.

Hematologic evaluation showed no abnormal findings. Gammaglobulin level was normal. Carcinoembryonic antigen (CEA, DAINABOT) value was 3.1 ng/ml, and alpha-protein was 8.9 ng/ml.

At operation, an anterolateral thoracotomy was performed through the 5th intercostal space. A greyish ball-shaped tumor was located in the lower anterior mediastinum contiguous to the pericardium, protruding into the right pleural cavity with invasion to the anterior lower chest wall. On palpation, there was a lung tumor in the superior segment of the right lower lobe with pleural indentation. During the operation, frozen section of the lung tumor was diagnosed as lung cancer (adenocarcinoma). Then the left lower lobectomy with mediastinal lymphadenectomy was performed. Anterior lower mediastinal tumor was resected with the invaded chest wall. The defect of the anterior chest wall was replaced with a one-folded Marlex-mesh® (DAVOL). The patient recovered well postoperatively without instability of the right chest wall during respiratory movement.

One year later, blephaloptosis recurred with double vision and the symptoms responded to Tensilon. Chest x-ray and CT scan showed no recurrence of the thymoma and lung cancer. Analysis of the T-cell subpopulations in the blood was normal. The titer of antibody against acetylcholine receptors in the serum was high (27 nmol/L). An occular type of myasthenia gravis was diagnosed and adequately controlled by prednisolone and Mytelase (Ambenonium chloride).

PATHOLOGY

The tumor which occurred at age 32 was located in the right lobe of the thymus, weighing 90 gm, measuring 11×7×7 cm in size. It was encapsulated by fibrous tissue which was slightly adherent to the pericardium and mediastinal pleura. However, it was

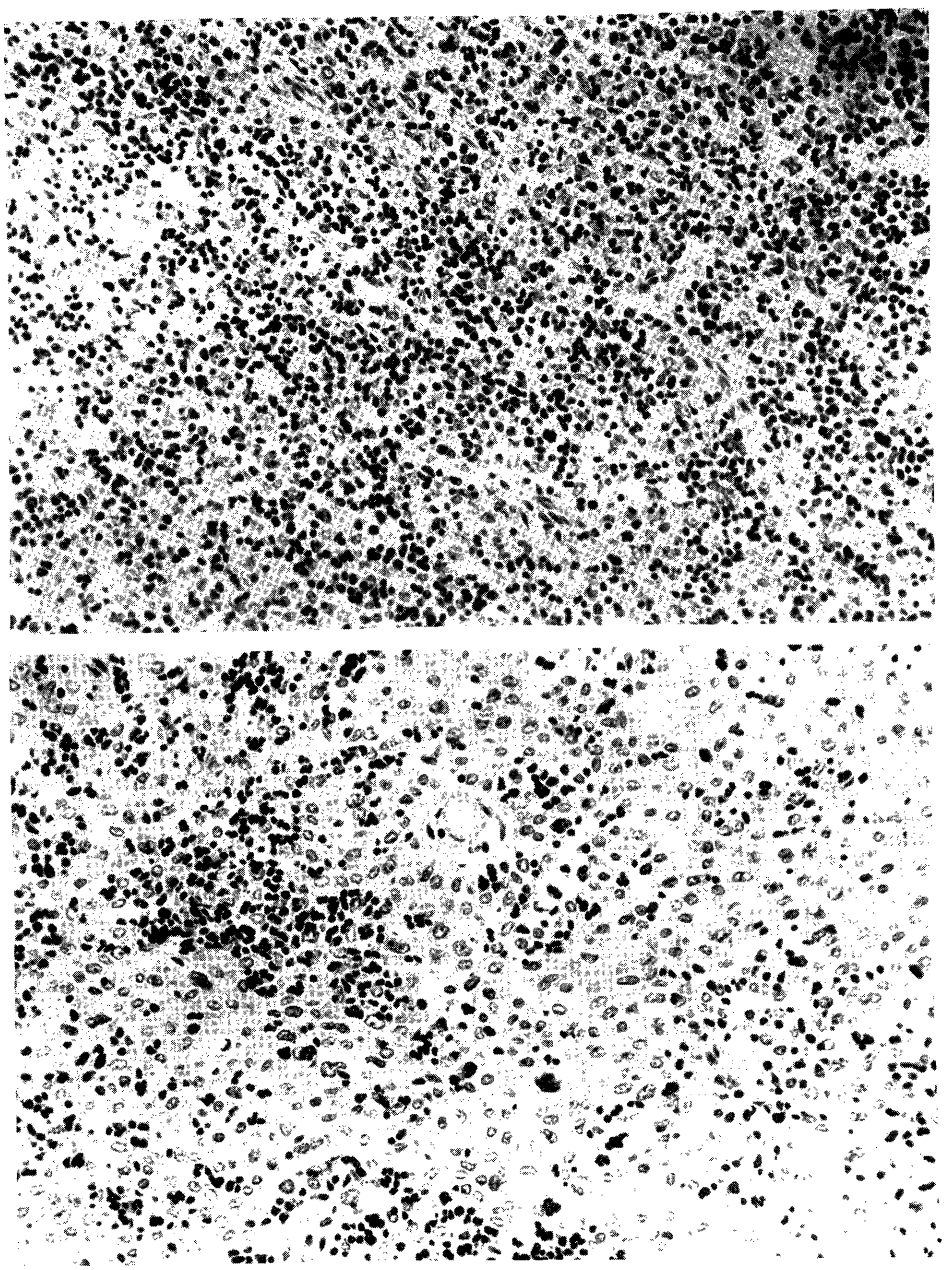

Fig. 1 <A> Photomicrograph of the primary thymoma showing lymphocytic predominance. (Hematoxylin-eosin, ×248)
<B> Photomicrograph of the recurrent thymoma showing mixed type. (Hematoxylin-eosin, ×248)

easily removed at operation. The cut surfaces were grey, solid with a cyst on the left measuring 2.5×2.5×2.0 cm. Microscopically, the tumor was lobulated by fibrous septa. The tumor lobules were composed of sheets of mature lymphocytes and sparse epithelial elements (Fig. 1, A). HASSALL's corpuscles were not identified in the tumor tissue. Tumor cells were confined to the capsule without infiltration.

The recurrent thymoma with the invaded chest wall were resected en block. The resected chest wall contained the 5th, 6th, 7th and 8th ribs as well as the intercostal muscles which were severed 2cm apart from the invaded margin of the thymoma. Microscopically, the tumor was irregularly lobulated by fibrous septa. The tumor lobules consisted of lymphocytes and epithelial cells (Fig. 1, B). The ratios of lymphocyte and epithelial cell were different from area to area but both components were usually intermingled. Tumor cells showed a slight degree of cellular pleomorphism and nuclear atypia without mitotic figures. Minimal invasion of tumor cells was found into the intercostal muscles.

The cut surfaces of the lung tumor were grey, measuring 2.5×2.5 cm. Microscopically, the tumor cells extended along the alveolar wall, partially showing a papillary pattern with moderate mucin production (Fig. 2). There were no metastases to the mediastinal or hilar lymph nodes.

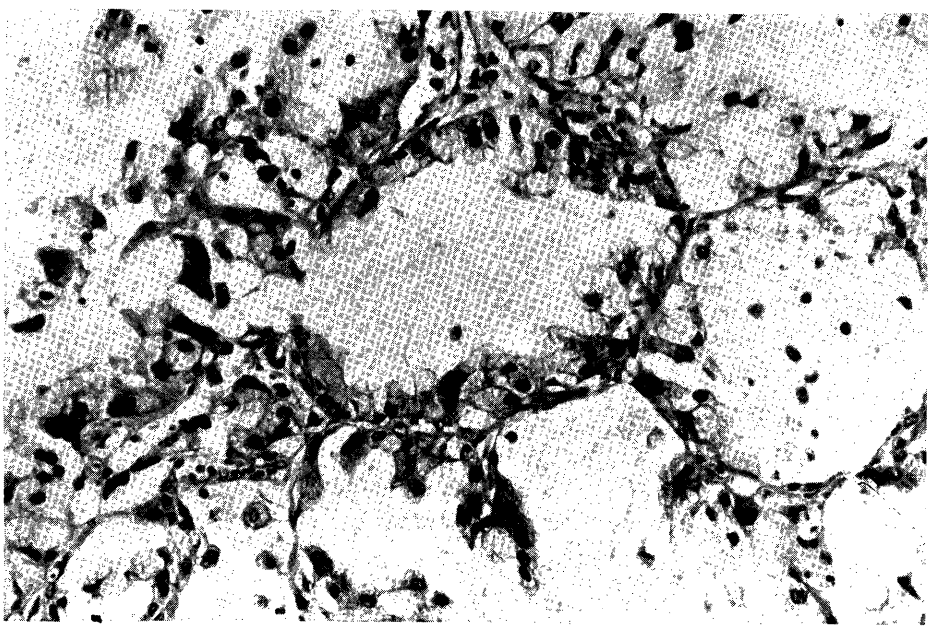

Fig. 2 Bronchiolo-alveolar adenocarcinoma. Tumor cells were growing along the alveolar wall with mucin production. (Hematoxylin-eosin, ×248)

DISCUSSION

Excluding germinal cell tumor, malignant lymphoma, carcinoid tumor, non-specific cyst and hyperplasia of thymus, 46 cases of thymoma were diagnosed and treated in our department from 1956 to 1983. Recurrence of non-invasive or encapsulated thymoma is rare. Among them only one of 30 non-invasive cases recurred after resection of thymoma. Based on a review of literature, 20 cases of recurrent non-invasive thymoma were collected.[1)-9)] All the patients were adults and the ages ranged from 22 to 64 years. The distribution of males and females were almost the same. About half of the cases were associated with myasthenia gravis. The time of recurrence ranged from 1 year 4 months to 19 years postoperatively. Recurrence of non-invasive thymoma usually occurred in two ways; (1) local recurrence in mediastinum or (2) pleural dissemination. In 2 cases,[1)] recurrences were seen both in mediastinum and pleura. Distant metastases of non-invasive thymomas to the supraclavicular region,[7)] axillary nodes,[8)] and cervical lymphnodes[6)] were also found.

Most of the intrathoracic metastatic form of thymoma are pleural dissemination. Pulmonary parenchymal metastases may occur as well.[10)11)] Since our patient had a history of thymoma, the mass shadows in the right lung field and mediastinum led to the preoperative diagnosis of recurrent thymoma with pulmonary metastasis.

Unusually, thymoma develops as multiple separate nodules in the thymic gland.[12)] Several ectopic thymomas have also been reported. The sites of local recurrence of the non-invasive thymomas in mediastinum varied from those of primary tumors in our case and 3 cases found in literature.[1)4)] It has been shown that thymic tissue exists in high frequency in the anterior mediastinum outside the capsule of the thymus.[13)] The facts suggest that undetected small thymoma in the thymus during operation or newly developed thymoma from the postoperative remnant of thymic gland may be considered as the causes of recurrent non-invasive thymoma including the presented case. It has been emphasized recently that low recurrence and high survival rates in the well-encapsulated cases and those without invasive growth into the surrounding organs are due to extensive excision of the tumor with surrounding tissues.[6)14)] To treat and prevent local recurrence of thymoma, complete removal of thymoma and thymic gland is warranted in both the cases associated with myasthenia gravis and those without myasthenia. It is considered that the operative procedure is the predisposing factor of pleural dissemination. However, pleural dissemination can occur spontaneously without surgical treatment. Preoperative radiotherapy had been used to prevent pleural dissemination. WEISSBERG *et al.* reported that none of the patients developed pleural metastasis after preoperative radiotherapy.[15)] Preoperative radiotherapy may decrease the incidence of pleural metastasis.

In five well-documented cases,[1)4)9)] histology of primary non-invasive and recurrent thymoma were all identical (2 lymphocytic, 3 mixed type). Only one case of mixed type recurred as a similar type but with malignant change (mitoses).[9)] In the present case, the histological types of the primary thymoma and recurrent thymoma were lymphocytic

and mixed type without mitotic figures respectively. We have no explanation about the difference of the histological types between primary and recurrent tumor.

Since SOUADJIAN[16] reported that incidence of non-thymic malignancy increases markedly in patients with thymoma, a few articles have described concomitant thymoma and extra-thymic malignancy. With the exception of the cases reported by SOUADJIAN, 33 patients were collected from literature. The distribution and sites of non-thymic malignancy are shown in Table 1. It has been suggested by LEGOLVAN[8] that there is an increased occurrence of second primary malignant neoplasms in patients with thymomas, particularly of the embryologically related thyroid gland. Though malignant lesions were observed more commonly in lung, bone marrow and thyroid gland, the number of cases is too small to conclude that malignancy is more prone to develop in those organs. Five of 33 patients developed neoplasms in 2 different sites as follows: (1) lung cancer and breast cancer,[5] (2) leukemia (bone marrow) and urinary bladder cancer,[22] (3) lymphoma (small intestine) and lung cancer,[19] (4) gastric cancer and lymphoma (lymph nodes),[30] (5) thyroid cancer and rectal cancer.[8]

Table 1. Distribution of non-thymic malignancy

Site	Cases
Lung	8
Bone marrow	8
(Leukemia)	(6)
(Myeloma)	(2)
Thyroid gland	5
Brain	2
Breast	2
Stomach	2
Tongue	1
Small intestine	1
Rectum	1
Colon	1
Urinary bladder	1
Liver (Lymphoma)	1
Inguinal & pulmonary lymphnodes (Lymphoma)	1
Arm (Fibrosarcoma)	1

(References 2-5, 8, 11, 17-32)

In the 33 thymomas associated with non-thymic neoplasms, 14 were non-invasive or well-encapsulated, 5 were invasive. There are no description about the macroscopic findings in the remaining 14 cases. It seems that progression of thymoma is not related to the incidence of non-thymic neoplasms.

Including the case presented herein, 9 lung cancers associated with thymoma have been reported. The histologic type of the thymoma were 1 epithelial, 1 lymphocytic, 3 mixed, 1 spindle cell and 3 unknown. The pathologic diagnoses of the lung cancers were squamous cell carcinoma 2 , adenocarcinoma 2, mucinous carcinoma 1 and unknown 4 . Analysis of these data discloses no obvious trend beween histological type of thymoma and histological type of lung cancer. The cause of the increased frequency of non-thymic malignancy in thymoma is not clear. It is considered that disturbance of immunological surveillance, states of immunodeficiency or immunosuppression are associated with an increased incidence of malignancy[33]. In our case, gammaglobulin level and T-cell subpopulations were normal.

Preoperative value of serum-CEA in the present case was 3.1 ng/ml (normal value:

below 2.5 ng/ml). Postoperative studies of serum-CEA were all less than 1.0 ng/ml. Elevation of serum-CEA level is well-known in most of patients of lung cancer. In our department, serum-CEA was studied in 7 cases of thymoma. Three of 7 were non-invasive, their CEA values were all below 2.5 ng/mg. In the 4 invasive thymomas, preoperative CEA values were 1.0, 2.6, 2.9 and 7.8 ng/mg. These data suggested that elevation of CEA may occur in thymoma. Although we are unable to define the elevation of CEA as to whether it is from thymoma or lung cancer in the present case, we believethat serum CEA may be an indicator of recurrence or progression of thymoma.

During follow-up of a surgical patient with thymoma, the possibility of a non-thymic malignancy must be kept in mind. It is reported that the highest incidence of non-thymic malignancy associated with thymoma is 10 to 15 years after the diagnosis of a thymoma[16]. In the long-term follow-up of resected thymoma, in addition to recurrent thymoma, screening for non-thymic malignancy is required.

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