

# Multimodal Treatment of Metastatic Thymic Carcinoma Including High-Dose Chemotherapy With Autologous Stem Cell Transplantation

## Report of a Case With More Than 4-Year Disease-free Survival

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Thymic carcinoma is a rare epithelial malignancy differentiated from thymoma by the presence of cytologically malignant cells. There are few reports of the treatment of locally advanced or metastatic thymic carcinoma. We describe a patient who sought treatment for thymic carcinoma metastatic to pleura, pericardium, retroperitoneum, and neck nodes. He was treated with neoadjuvant etoposide, ifosfamide, and cisplatin, and underwent resection. We then administered high-dose chemotherapy with autologous stem cell support, followed by radiation therapy. The patient remains in complete remission more than 4 years after diagnosis. To our knowledge, this is the first report of metastatic thymic carcinoma treated with neoadjuvant therapy and postoperative high-dose chemotherapy. Metastatic thymic carcinoma may be curable by aggressive combined therapies.

**Key Words:** Thymic carcinoma—Neoadjuvant—High-dose chemotherapy—Radiation therapy.

Thymic carcinomas are rare neoplasms derived from the thymic epithelium that are characterized by locoregional invasion of mediastinal structures and metastatic spread to lungs, bone, and liver.<sup>1</sup> They differ histologically from thymomas by the presence of malignant cytologic features.<sup>2</sup> The prognosis for patients with thymic carcinoma is poor even when the tumor is localized. A median survival time of 25.5 months was reported in 20 consecutive cases where curative resection was attempt-

ed.<sup>1</sup> Cisplatin-based chemotherapy showed activity in a series of five patients with metastatic thymic carcinoma.<sup>3</sup> Combined chemotherapy, radiotherapy, and surgery has been used with some success in unresectable malignant thymomas.<sup>4-6</sup> We decided to attempt a similar approach in treating metastatic thymic carcinoma, but with more dose-intense chemotherapy, i.e., high-dose chemotherapy with autologous peripheral stem cell support (HDCT-PSCS). To our knowledge, there have been no previous reports of front-line multimodal treatment of thymic carcinoma that included HDCT-PSCS. The patient described here is alive and free of disease more than 4 years after diagnosis.

### CASE REPORT

A 21-year-old man was referred to the hospital because of an enlarging neck mass. He complained of shortness of breath and chest pain without fever, night sweats, or weight loss. On physical examination, temperature was 37.1°C, blood pressure 120/80 mm Hg, pulse 64 beats/min, respiration 18/min. His chest was asymmetric, with the left side more prominent than the right and decreased breath sounds over the left lung. There was a firm, 3 × 4-cm mass on the lower left part of the neck. No other adenopathy was detected. Nasopharyngeal examination revealed nothing abnormal. The abdomen was soft with no hepatosplenomegaly, and there were no testicular masses. The chest radiograph showed a large anterior mediastinal mass (Fig. 1). Electrocardiogram showed a normal sinus rhythm with an inverted T-wave in lead AVL. Complete blood count,  $\alpha$ -fetoprotein, and  $\beta$ -human chorionic gonadotropin were normal, as was the urinalysis. The erythrocyte sedimentation rate was 13 mm/h, and his blood chemistry was within normal limits except for total protein of 9.2 g/dl (normal: 5.3-8 g/dl) and lactate dehydrogenase

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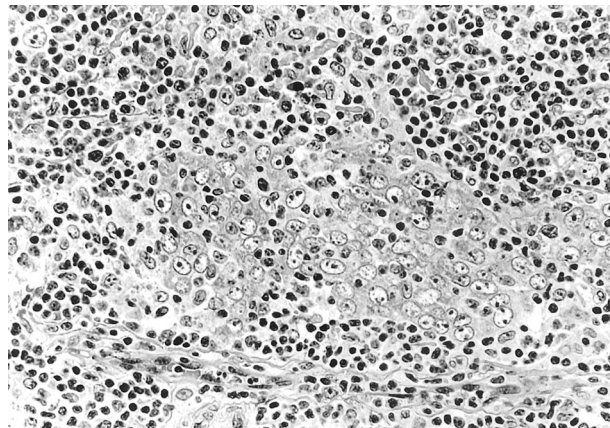
**FIG. 1.** Chest radiograph at presentation showing a huge mediastinal mass.

of 689 U/l (normal: 270–530). Serum protein electrophoresis showed normal results.

Computed tomography showed a mediastinal mass of varying density,  $20 \times 12 \times 14$  cm, displacing the trachea, esophagus, and heart to the right extending into the superior mediastinum (Fig. 2). A left pleural effusion was noted. The spleen was moderately enlarged with a normal-sized liver. Enlarged retroperitoneal and retrocaval nodes were also seen. Bone marrow aspiration and biopsy results were normal. Incisional biopsy of the left neck mass was



**FIG. 2.** Computed tomography section at the level of the first thoracic vertebral body showing a left superior mediastinal mass extending into the soft tissues of the neck with deviation of the trachea to the right.



**FIG. 3.** Photomicrograph of section from cervical lymph node. Metastatic carcinoma is shown in center, with small round lymphocytes surrounding and interspersed with the tumor.

performed, analysis of which indicated thymic carcinoma of the lymphoepithelial cell type (Fig. 3).

The patient was treated with a chemotherapy combination of cisplatin  $20 \text{ mg/m}^2/\text{d}$ , ifosfamide  $1.2 \text{ g/m}^2/\text{day}$  with mesna, and etoposide  $100 \text{ mg/m}^2/\text{d}$  during 5 days every 3 weeks (VIP) for 4 cycles, with granulocyte colony-stimulating factor support during all cycles. Total regression of the neck mass was noted on physical examination after the first cycle. Greater than 50% reduction in the volume of the mediastinal mass with normalization of spleen and retroperitoneal nodes were seen on computed tomography after 2 cycles. The chest radiographs after the third and fourth cycles were identical, suggesting that maximal response had been achieved (Fig. 4). The last two cycles were given at 75% of the ideal dose because of grade IV thrombocytopenia.

In June, 1996, after recovery from chemotherapy, he underwent midsternotomy, which revealed considerable scar tissue, containing scattered areas of residual mass, adherent to the great vessels, aortic arch, pericardium, and hilum of the left lung. The tumor was resected from the lower part of the neck, thymus, left innominate vein, and aortic arch. In addition, partial pericardiectomy was performed to resect adherent masses. The surgeon's intraoperative impression was that 98% of the tumor was excised. After insertion of chest drains, a hyperthermic ( $40.7^\circ$ ) pleural perfusion with cisplatin 150 mg in 3,500 ml of Hartman's solution was performed for 1 hour. Histologic examination of resected specimens showed mostly fibrosis, necrosis, and reactive changes with a few areas of carcinoma consistent with lymphoepithelial-type thymic carcinoma in the resected pericardium and thymus.

After recovery from surgery, the patient received HDC with carboplatin 400 mg/d on days 1 to 4, thiotepa 120 mg/d on days 1 to 3, etoposide 400 mg/d, and melphalan 120 mg/d on days 1 to 2; supported by granulocyte colony-stimulating factor mobilized autologous periph-



**FIG. 4.** Chest radiograph after three cycles of chemotherapy demonstrating marked decrease in the size of the mediastinal mass.

eral blood stem cells. He was treated with broad-spectrum antibiotics for several days because of fever, and briefly had paralytic ileus but had an otherwise uneventful course. Subsequently, he was given radiotherapy, 4,500 cGy in 180-cGy fractions, delivered anteriorly–posteriorly to the mediastinum, pericardium, left supraclavicular area, and left lower part of the neck. The spinal cord was shielded posteriorly after 3,780 cGy. He has been in continuous complete remission since resection.

## DISCUSSION

Thymic carcinoma is differentiated histologically from thymomas by cytologically malignant features. The two major types of thymic carcinomas are well-differentiated squamous cell carcinomas and the higher grade, poorer prognosis lymphoepithelioma-like carcinoma.<sup>2</sup> Staging of thymic carcinoma has been traditionally according to the Masaoka system, based on operative findings, with hematogenous or lymphogenous spread as in our patient defined as stage IVb.<sup>7</sup> In a series of 43 patients undergoing surgery for thymic carcinoma during a 45-year period, overall survival at 5 and 10 years was 65% and 35%, respectively, with a recurrence rate of 65% at 5 years.<sup>8</sup> Thymic carcinoma has been shown to be responsive to cisplatin-based chemotherapy, with Wiede et al. achieving a complete response in two patients and a partial response in a third patient with

metastatic thymic carcinoma treated with cisplatin, bleomycin, and etoposide.<sup>3</sup> The combinations of cyclophosphamide–doxorubicin–cisplatin and etoposide–cisplatin have shown activity in thymomas, both locally advanced and metastatic.<sup>4–6,9</sup> Because of the potential for excessive cardiopulmonary toxicity when combined with mediastinal radiotherapy and surgery, we did not use doxorubicin or bleomycin. We thought that ifosfamide would be a more appropriate agent than cyclophosphamide because of its effectiveness with cisplatin in relapsed lymphomas.<sup>10</sup> Subsequent to our treatment of this patient, a report was published on the efficacy of ifosfamide as a single agent in locally advanced and metastatic thymoma.<sup>11</sup> Intrapleural hyperthermic chemotherapy has been reported to be of benefit after resection in non–small-cell lung cancer.<sup>12</sup> We believed that our patient with minimal residual disease after resection in and around the pleura might similarly benefit.

There are little published data on HDC for thymic tumors, and to our knowledge no reports of its use as front-line therapy. The use of HDCT-PSCS was described in abstract form<sup>13</sup> in five patients with either progressive thymic carcinoma after first-line conventional therapy or recurrent thymoma. No long-term survival was achieved for the patients with thymic carcinoma, and no advantage over conventional-dose salvage therapy was observed in the patients with recurrent thymoma.<sup>13</sup>

In conclusion, we treated a patient with metastatic thymic carcinoma with neoadjuvant combination chemotherapy (VIP), aggressive surgery, intrapleural hyperthermic cisplatin, consolidation HDCT-PSCS, and radiotherapy. As in other chemotherapy-sensitive tumors, initial intensive therapy may produce long-term survival even at advanced stages of disease. Although the disease is too rare for a prospective randomized trial to be practical, we suggest that patients with locally advanced or metastatic thymic carcinoma be treated initially with chemotherapy. Resection of local–regional disease, with or without intrapleural chemotherapy, should then be attempted, after regression of distant metastases. If complete or near-complete response can be achieved by neoadjuvant chemotherapy and surgery, HDCT-PSCS and radiation consolidation should be initiated. ©

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