Remission of Invasive Thymoma due to Chemotherapy*

Two Patients Treated with Cyclophosphamide, Doxorubicin, and Vincristine

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Information regarding the effectiveness of chemotherapy in cases of invasive thymoma is limited. Two patients in whom the combination of cyclophosphamide, doxorubicin, and vincristine produced remission of invasive thymoma are described. The durations of remission were eight and seven months, respectively. In both patients, recurrence was observed at the site of bulky disease, and a secondary complete response continuing for 37 months was achieved in one of them with radiation therapy.

Surgery and irradiation have been the primary treatments for patients with invasive thymoma. The role of chemotherapy in treating patients with thymoma is not well defined; however, recent reports of complete responses to cisplatin alone and to regimens of combined chemotherapy suggest that this tumor might be relatively sensitive to cytotoxic drugs.

We have observed two complete remissions which resulted from treatment with relatively low dosages of cyclophosphamide, doxorubicin, and vincristine. One patient had intrathoracic recurrence only, and the other had disseminated disease involving the liver and lungs. The potential role of chemotherapy and its relationship to radiation therapy are discussed.

Case Reports

Case 1

In September 1978, a 52-year-old white woman presented with menorrhagia of six months' duration. She had no other complaints, and the findings from physical examination were unremarkable. Uterine dilatation and curettage revealed well-differentiated adenocarcinoma of the endometrium. A chest roentgenogram at that time disclosed an anterior mediastinal mass. Prior to definitive therapy for the uterine tumor, left thoracotomy was performed, and biopsy of the mediastinal mass revealed malignant lymphoepithelial thymoma. The mediastinal tumor was intimately related to residual thymic tissue. Histologically, no resemblance to the endometrial tumor could be found, with the mediastinal tumor revealing fine fibrovascular septae which separated the cells into cords and bundles on histologic examination. The cells of the tumor were large, and their morphologic form varied from round to spindle.

Nuclide scans of liver, brain, and bone were unremarkable. The patient received 3,200 rads to the pelvis starting in October 1978. Following completion of the pelvic irradiation, a sternotomy with partial resection of the mediastinal tumor was performed in November 1978. The tumor had invaded the surrounding tissue, with involvement of the left phrenic nerve, pulmonary artery, pleura, and pericardium. Because the thymic tumor was incompletely resected, mediastinal irradiation was given after surgery. This treatment consisted of 3,000 rads in 15 fractions given through an anterior-posterior portal, followed by 3,000 rads in 15 fractions given by an oblique beam. In December 1978, treatment of the endometrial cancer was completed by performing a hysterectomy; only residual superficial endometrial carcinoma was found.

In April 1979, an asymptomatic 8 x 11-cm pleural-based mass was noted in the left thorax on the chest x-ray film (Fig 1A) and computerized tomographic scan (Fig 1C). A gallium scan demonstrated increased activity in the same region (Fig 1B). Percutaneous needle biopsy of this mass demonstrated lymphoepithelial thymoma. Additional radiation therapy was not feasible at this time because the field of treatment would have overlapped previously irradiated areas. Therefore, starting on May 4, 1979, doxorubicin (30 mg/sq m), cyclophosphamide (500 mg/sq m), and vincristine (1 mg/sq m) were administered intravenously every 21 days. Three months later, both the chest x-ray film (Fig 2A) and gallium scan (Fig 2B) were improved. The computerized tomographic scan revealed resolution of the mass, with only minimal pleural irregularity (Fig 2C). Chemotherapy was discontinued after six courses, two cycles after complete remission had been achieved.

Five months after observing complete regression of the tumor (eight months after initiation of chemotherapy), a 6 x 4-cm lesion was observed on the chest x-ray film, which was confirmed on gallium scan. Prednisone (200 mg daily for five consecutive days) and bleomycin (15 mg intravenously) were added to the previous regimen. The mass decreased to 2 x 2 cm after two cycles. Doxorubicin was discontinued in July 1980 at a cumulative dosage of 425 mg/m². A month later, the patient presented with congestive heart failure, presumably secondary to doxorubicin-induced cardiomyopathy, and all chemotherapy was stopped. Within two months, progression of the tumor was again noted, and a single course of cisplatin (50 mg/sq m), cyclophosphamide (700 mg/sq m), and vincristine (1 mg/sq m) was administered without response. In November 1980, a total of 3,000 rads was administered to the left pleural mass. No tumor was detectable on the chest x-ray film one month after completion of irradiation. The patient remains asymptomatic and without evidence of disease as documented by chest x-ray films and gallium scan 37 months after receiving radiation therapy and 54

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Roentgenogram depicts left pleural-based mass which was present immediately prior to starting chemotherapy in case 1. This mass was confirmed on gallium scan (B, middle) and thoracic computerized tomogram (C, bottom).

Figure 1. A (top), Roentgenogram depicts left pleural-based mass which was present immediately prior to starting chemotherapy in case 1. This mass was confirmed on gallium scan (B, middle) and thoracic computerized tomogram (C, bottom).

Figure 2. A (top), Chest x-ray film after four cycles of chemotherapy demonstrated significant regression in mass of tumor. Repeat gallium scan (B, middle) and computerized tomographic scan (C, bottom) demonstrate resolution, with only minimal pleural irregularities noted on computerized tomographic scan in left hemithorax.

In February 1981, a 66-year-old Oriental woman presented with cough and increasing exertional dyspnea which had been present for months after the diagnosis of recurrence.

CASE 2

In February 1981, a 66-year-old Oriental woman presented with cough and increasing exertional dyspnea which had been present for
Distant metastases are rare, and frequently, the treatment of intrathoracic recurrence is difficult, not only because reexcision may not be possible due to the location or to the extent of the tumor, but also because previous radiation therapy may preclude retreatment in the same treatment port. In these situations where local control is inadequate, as well as in the rare cases presenting with distant disease, chemotherapy might prove beneficial.

Little is known about the chemosensitivity of thymomas. Many investigators have included glucocorticoids alone or in combination with other agents for the treatment of thymoma. Recent ultrastructural, immunologic, and functional investigations indicate lymphocytes isolated from thymomas are nonneoplastic in origin. The neoplastic cells are believed to be derived from the epithelial component. Although not always clearly stated, the majority of clinical responses seen with glucocorticoids alone or in combination with other agents have been in tumors with a lymphocytic component (ie, lymphocytic or lymphoepithelial subtypes). As corticosteroids may produce a lympholytic effect, regression of tumor therefore may not truly
represent antineoplastic effect in patients with a lymphocytic component.

In the few numbers of cases successfully treated with nonsteroid-containing chemotherapy, cisplatin has demonstrated activity. Indeed, during a phase-I trial of cisplatin, the only partial remission noted was in a patient with a thymoma which lasted 13 months. Subsequent reports of responses to cisplatin alone or as part of a combined regimen have been recently detailed by several authors. In three of these cases, complete remissions were demonstrated, lasting from 10 to 24 months.

Chemotherapeutic regimens not containing cisplatin have been utilized in only a small number of patients. With the exception of a complete remission achieved with doxorubicin and cyclophosphamide, the majority of these responses have been incomplete and of brief duration. Although this report confirms the activity of doxorubicin and cyclophosphamide (combined chemotherapy) for metastatic thymoma, the duration of remissions were relatively brief in these cases, compared to those reported with cisplatin. In both cases presented in this report, tumor recurred at the site of bulky disease. As irradiation has been reported to produce prolonged remissions in invasive thymoma, its role in management of this disease should not be overlooked. In case 1, radiation therapy for intrathoracic recurrence was initially not feasible because of an increased risk of complications from overlapping fields of treatment. Subsequent to a response to chemotherapy, additional radiation therapy could be administered safely to the site of recurrent tumor. The sustained complete remission in this case suggests that consolidation with radiation therapy may be beneficial in selected patients following maximal response to chemotherapy.

In summary, this report provides further evidence that invasive thymoma is a chemosensitive tumor. A prolonged second remission with the addition of further radiation therapy (case 1) was also noted. Additional data regarding sensitivity of thymomas to chemotherapy are needed and should become available from at least two ongoing cooperative group trials evaluating cisplatin alone (Eastern Cooperative Oncology Group) and the combined regimen of cisplatin plus doxorubicin plus cyclophosphamide alone (extensive disease) or with radiation therapy (limited disease) by the Thymoma Intergroup Study.

REFERENCES