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Oncologist 2006;11:887-894
DOI: 10.1634/theoncologist.11-8-887

This information is current as of September 8, 2006

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Thymoma: Benign Appearance, Malignant Potential

RICHARD F. RIEDEL, a,c WILLIAM R. BURFEIND JR b,c

aDivisions of Medical Oncology and Hematology and bDivision of Thoracic Surgery, Duke University Medical Center, Durham, North Carolina, USA; cThe Ruth & Herman Albert Thoracic Oncology Program, Duke Comprehensive Cancer Center, Durham, North Carolina, USA

Key Words. Thymoma • Surgery • Adjuvant radiation • Chemotherapy • Paraneoplastic syndromes

ABSTRACT
Thymoma is a rare tumor with a largely indolent growth pattern. It does, however, have malignant potential as a result of its ability to invade locally and metastasize regionally. Often associated with a number of immune- and nonimmune-mediated paraneoplastic syndromes, patient outcomes are directly related to stage of disease and the ability to achieve a complete surgical resection. Surgery is the mainstay of treatment, with adjuvant radiation recommended for invasive thymoma. Sensitive to both chemotherapy and radiation, durable responses are achievable in incompletely resected and inoperable patients. We present two cases of thymoma followed by a general discussion with an emphasis on treatment for both early and advanced-stage disease. The Oncologist 2006;11:887–894

CASE PRESENTATION 1
A 62-year-old woman, with no significant past medical history, presented to her primary care physician in November of 2005 for a routine physical exam. A chest x-ray was performed, in the absence of symptoms, which surprisingly revealed a right paramediastinal mass. Computed tomography (CT) scan of the chest revealed a 5.3 × 3.0-cm mass in the anterior mediastinum (Fig. 1) with hypermetabolic activity by positron emission tomography (PET) scan. Fine-needle aspiration (FNA) performed at an outside hospital revealed a spindle-cell neoplasm consistent with thymoma. Routine laboratory studies were unrevealing, with the exception of quantitative immunoglobulins, which revealed decreased levels of IgA (68 mg/dl; normal range, 81–463), IgG (393 mg/dl; normal range, 694–1,618), and IgM (<5 mg/dl; normal range, 48–270). The patient was referred to the thoracic oncology program at our institution for evaluation and treatment.

CASE PRESENTATION 2
A 45-year-old Caucasian woman, with no significant past medical history, presented to an outside tertiary care facility in June of 2001 with complaints of slurred speech, difficulty swallowing, and blurry vision, and was diagnosed with myasthenia gravis. As part of the evaluation, imaging of the chest was performed, revealing a 10-cm right costophrenic mass with associated pleural-based lesions. The patient was referred to a thoracic surgeon who performed a thoracoscopic biopsy of a pleural-based mass, revealing lymphocyte-rich thymoma. She was deemed inoperable and received six cycles of cisplatin, doxorubicin, and cyclophosphamide (PAC) chemotherapy followed by radiation therapy. She had a durable response for 4.5 years and was followed with serial CT scans every 6 months. The most recent CT scan performed in December of 2005 revealed a right anterolateral pleural-based lesion (Fig. 2), which had increased in size from prior examination and was hypermetabolic by PET...
An FNA was performed, revealing recurrent thymoma. The patient was referred to the thoracic oncology program at our institution for evaluation and treatment.

**DISCUSSION**

**Introduction**

Thymoma refers to a malignancy arising from epithelial cells of the thymus. It accounts for 20% of mediastinal tumors and is the most common tumor of the anterior mediastinum, accounting for approximately 50% of all tumors in adults. Ninety percent of all thymomas occur in the anterior mediastinum, with the remainder occurring in the neck or other mediastinal areas [1]. Overall, however, it is considered a rare malignancy, with an incidence of 0.15 cases per 100,000 [2]. Although considered to have an indolent growth pattern, thymoma has the ability for both local invasion and intrathoracic recurrences [3]. As a result, the evaluation and treatment of these tumors, particularly in locally advanced disease, requires a multidisciplinary approach to improve long-term patient outcomes.

**Anatomy and Embryology**

The thymus gland is an anterior mediastinal structure arising embryologically from the third pharyngeal pouch. A prominent organ early in life, the thymus reaches a maximum size of 40 g during puberty before regressing and involuting during adulthood, being replaced by fibrofatty tissue. The thymus gland contains both epithelial and lymphocytic components. The epithelial cells are predominantly medullary in location, while the lymphocytes are predominantly cortical. The lymphocytic component represents an admixture of lymphocytes that originate from the bone marrow and migrate to the thymus for further processing and maturation. The stroma of the thymus contains the epithelial cell component.

**Clinical Presentation and Imaging**

Thymomas typically present in the fourth or fifth decade of life and exhibit no gender predilection. Half of thymomas present asymptptomatically and are detected incidentally on radiographic imaging, as in case 1, while half will present with symptoms associated with a paraneoplastic syndrome, as in case 2, or with symptoms attributable to the local mass effect. The most common symptoms of local tumor growth are cough, vague chest pain, dyspnea, and symptoms attributable to superior vena cava syndrome.

Imaging is an essential part of the workup and in conjunction with history and physical exam is often the only investigation needed prior to treatment. Following identification of a mediastinal mass on chest x-ray, a CT scan of the chest should be obtained. CT allows for the characterization of tumors as well as an assessment of possible invasion into surrounding structures. Contrasted studies are preferred to assess vascular invasion and cystic components [4]. Dynamic magnetic resonance imaging (MRI) has been examined as a potential way to improve staging and differential diagnosis determination [5], and PET has been examined for tumor detection and differentiation between invasive and noninvasive thymoma with mixed results [6–8].

**Differential Diagnoses**

For patients presenting with mediastinal masses, an extensive differential should come to mind (Table 1). This differential can be narrowed, in part, based on anatomic location and patient characteristics. Anterior mediastinal masses...
include thymoma, germ cell tumors, lymphoma, thymic carcinoma, and masses arising from the thyroid. Tumors that can arise directly from the thymus include thymoma, lymphoma, carcinoid, thymolipoma, and thymic carcinoma.

Differentiating malignant thymoma from the more aggressive thymic carcinoma is extremely important. In contrast to the bland cytologic appearance of malignant thymoma, thymic carcinoma exhibits aggressive cytologic features with evidence of mediastinal invasion in the majority of patients. Histologically, thymic carcinomas exhibit cellular atypia, increased proliferative capacity, and anaplastic features [9]. Radiographically, thymomas are more likely to exhibit smooth contours and a round shape by CT than thymic carcinomas, which more commonly exhibit irregular contours [10].

Pathology and Classification
Thymomas are characterized histologically by the presence of malignant epithelial cells with an associated admixture of nonmalignant lymphocytes. A fibrous capsule surrounds the tumor and is associated with thick fibrous bands, providing a lobular appearance [11]. The epithelial cells may either be elongated, spindle-shaped cells or ovoid and polygonal in appearance. Importantly, the malignant epithelial cells lack features typically characteristic of malignancy. As a result, thymomas generally have bland cytological features. The malignant behavior of thymoma is based on observed invasion either macroscopically into surrounding organs and structures or microscopically through the thymus capsule. Approximately 30%–40% of thymomas are invasive [12].

Several classification schemes have previously been developed for thymoma. Original classification systems focused on descriptive naming. The original classification system proposed by Bernatz et al. [13] used dominant cell type to classify thymomas as either epithelial, lymphocytic, mixed, or spindle-cell type. This classification system, however, did not have significant clinical relevance. As a result, a new classification by Levine and Rosai [14] used both clinical stage and cellular atypia. Marino and Muller-Hermelink [15] developed an alternative classification system reflecting both anatomic and functional aspects of the thymus gland. In order to provide some degree of standardization, the World Health Organization (WHO) committee proposed a new classification system for thymomas and carcinomas arising from the thymus [16]. The current classification system is a histologically based system classifying thymoma into two major classes based on the appearance of the malignant epithelial cells, spindle shaped (type A), or epithelioid (type B). Five thymoma classes are recognized in the WHO system (Table 2). The WHO classification was shown, in recent studies, to have prognostic significance [17–21]. As an example, thymoma classes A and AB have been associated with less invasive and aggressive clinical courses than class B thymomas [11].

Staging
Stage has additionally proven to have prognostic significance. Although classically felt to have an indolent growth pattern, thymoma has malignant potential, as evidenced by its invasive ability. The Masaoka Staging System is the most commonly used system to assess stage in thymoma (Table 3) [22]. Modifications to the original have since been offered including a tumor/node/metastasis (TNM)-based system but none have provided significant advantages over the original [23, 24]. Unlike the TNM systems used for most cancer staging, the Masaoka staging system is based on the degree of invasiveness (Table 3). Stage I tumors are completely encapsulated with no evidence of microscopic or macroscopic invasion. Stage II tumors have evidence of microscopic capsular invasion or macroscopic invasion into surrounding fat or pleura. Stage III tumors invade locally into surrounding structures, such as the lung, great vessels, and mediastinal structures, while stage IV tumors present with more distant lymphatic or hematogenous metastases.

Paraneoplastic Syndromes
Thymomas exhibit a unique biology and are associated with a number of paraneoplastic disorders. Although a variety of immune, nonimmune, and endocrine disorders have been

<table>
<thead>
<tr>
<th>Anterior</th>
<th>Middle</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoma</td>
<td>Castleman's disease</td>
<td>Neurogenic tumor</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>Lymphoma</td>
<td>Vertebral lesion</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Pericardial cyst</td>
<td>Bronchogenic cyst</td>
</tr>
<tr>
<td>Germ cell</td>
<td>Bronchogenic cyst</td>
<td>Enteric cyst</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Metastatic cyst</td>
<td>Xanthogranuloma</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Systemic granuloma</td>
<td>Vascular/arch anomalies</td>
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<td>Thyroid/goiter</td>
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<td>Vascular</td>
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reported, the most common associations are with myasthenia gravis (MG), pure red cell aplasia (PRCA), and hypogammaglobulinemia.

MG is characterized by the development of autoimmune antibodies to the acetylcholine receptor on postsynaptic neuromuscular junctions. Patients often present with blurred vision, dysphagia, and muscle weakness. MG is associated with approximately 30% of thymoma cases, and most patients with MG have some degree of thymic abnormality, specifically, thymic hyperplasia (60%–70%) or thymoma (10%–12%) [25]. A recent assessment of autoantibody profiles and neurological correlations in patients with thymoma identified antibodies to the acetylcholine receptor in all patients with thymoma-associated MG [26]. Interestingly, surgical resection of thymoma often results in an improvement in MG-related symptomatology [27].

PRCA is the second most common paraneoplastic syndrome associated with thymoma and results from an immune-mediated suppression of erythropoiesis. Autoreactive erythroid progenitor suppressor T cells have been reported in patients with PRCA and thymoma [28]. PRCA occurs in approximately 5%–10% of thymoma patients, with 50% of PRCA patients having a thymoma [12]. Similar to MG, laboratory studies may improve after surgical resection in up to 40% of patients [12, 29].

Hypogammaglobulinemia in association with thymoma occurs in 3%–6% of patients and is referred to as Good’s syndrome [30]. Patients exhibit a combined B- and T-cell immunodeficiency and are susceptible to recurrent infections, with sinusopulmonary infections secondary to encapsulated organisms being most common [31, 32]. The pathogenesis of the disorder is unknown, but may be related to T-cell–mediated immunosuppression or due to cytokines, perhaps produced in the bone marrow, that influence both thymic and B-cell precursor growth and differentiation [32]. Primary treatment is surgical resection of the tumor.

Unlike MG and PRCA, treatment of hypogammaglobulinemia results in inconsistent improvements in immunoglobulin levels [29].

### Treatment

#### Surgery

The mainstay of treatment for thymoma is surgery; with the goal of achieving a complete surgical resection (R0) being the main determinant of survival. Routine biopsy of encapsulated lesions is not recommended. Instead, complete surgical resection should be performed. If an induction strategy for more advanced disease is being considered, or a diagnosis other than thymoma is likely, biopsy is recommended to confirm diagnosis.

Five and 10-year survival rates approximate 100% and 95%, respectively, for stage I, 91% and 81%, respectively, for stage II, and 74% and 46%, respectively, for stage III disease [17]. Five-year survival rates for stage IV disease are <25% [33]. Patients should be explored through a complete median sternotomy with en bloc removal of the entire thymus and mediastinal fat from phrenic nerve to phrenic nerve and from diaphragm to brachiocephalic vein. For invasive stage III tumors, en bloc resection of the pericardium, brachiocephalic vein, superior vena cava, lung, and up to one of the phrenic nerves can be performed. If pleural or lung metastases are discovered, these should be resected.

Debate has ensued over the role of subtotal resection when complete resection cannot be performed. Across a series of studies, 10-year survival rates for patients achieving a complete surgical resection (R0) being the main determinant of survival. Routine biopsy of encapsulated lesions is not recommended. Instead, complete surgical resection should be performed. If an induction strategy for more advanced disease is being considered, or a diagnosis other than thymoma is likely, biopsy is recommended to confirm diagnosis.

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Debate has ensued over the role of subtotal resection when complete resection cannot be performed. Across a series of studies, 10-year survival rates for patients achieving a complete surgical resection averaged 75%. In contrast, the average 10-year survival rate in partially resected patients was 39%, approaching the 33% observed with biopsy alone [34]. There is at least some controversy here, because several reports show superior results with partial resection over biopsy [35–38]. Tumor debulking, however, when compared with biopsy alone in a retrospective study, showed no better prognosis when followed by radiation therapy [39].
For patients with advanced disease, induction strategies have been investigated, with a goal of attempted surgical resection post-therapy [40–45]. The final results of a phase II study investigating the results of a multidisciplinary approach in patients with unresectable malignant thymoma were recently reported (Table 4) [43]. A strategy of induction chemotherapy followed by surgical resection, postoperative radiation, and consolidation chemotherapy produced a major response in 17 (77%) of 22 patients, including three (14%) complete responses and 14 (63%) partial responses. R0 surgical resection was achieved in 16 (76%) patients previously deemed inoperable, and incomplete resection was achieved in five (24%). The overall survival rates were 95% at 5 years and 79% at 7 years. As a result, patients with disease initially deemed inoperable warrant a trial of induction therapy followed by a reassessment and consideration of surgery, recognizing the prognostic significance associated with complete surgical resection.

**Adjuvant Radiation Therapy**

Adjuvant therapy, specifically, postoperative radiation, is often recommended for invasive thymoma regardless of resection status. Quality evidence supporting this recommendation, however, is limited. In fact, no prospective randomized trial has been performed assessing the efficacy of adjuvant radiation for resected thymoma.

Recurrence rates in stage I disease are extremely low and approximate the rates seen in patients who receive observation alone [46–49]. As a result, adjuvant radiation in this setting is not warranted, assuming complete resection is achieved. The role of radiation therapy in completely resected stage II disease, however, is debated. The published literature is largely retrospective, of limited sample size, and shows conflicting results [33, 35, 46–50]. In a retrospective series by Singhal et al. [51], no survival advantage for the addition of adjuvant radiation therapy was seen in patients with completely resected stage II disease. Mangi et al. [52] have similarly shown no significant difference in local or distant recurrence rates in completely resected stage II patients who received radiation therapy. In contrast, 6 of 18 completely resected, nonirradiated stage II patients (33%) experienced a mediastinal relapse in a study by Curran et al. [48].

Data supporting a role for adjuvant radiation therapy in the incompletely resected patient are more robust. Curran et al. [48] identified a mediastinal relapse rate of 21% in stage II or III patients who received subtotal resection or biopsy and radiation, compared with 53% for those who received surgery alone. Strobel and colleagues [53] identified a recurrence rate of 34% in a series of patients who received adjuvant radiochemotherapy, compared with 78% in those not receiving adjuvant therapy. Importantly, stage III patients who receive incomplete resections, even after receiving postoperative radiation therapy, have statistically significant lower 5- and 10-year survival rates than those who receive complete resection (28% and 14% vs. 28% and 14%, respectively; \( p = .002 \)) [54].

**Advanced Disease**

In the metastatic or recurrent setting, thymoma exhibits sensitivity to a number of single agents including cisplatin, ifosfamide, doxorubicin, cyclophosphamide, and corticosteroids. Studies are small, however, and limited by potential bias. Combination therapy has shown an ability to produce prolonged durable responses in thymic tumors. A prospective intergroup trial explored PAC chemotherapy in patients, and shows conflicting results [33, 35, 46–50]. In a retrospective series by Singhal et al. [51], no survival advantage for the addition of adjuvant radiation therapy was seen in patients with completely resected stage II disease. Mangi et al. [52] have similarly shown no significant difference in local or distant recurrence rates in completely resected stage II patients who received radiation therapy. In contrast, 6 of 18 completely resected, nonirradiated stage II patients (33%) experienced a mediastinal relapse in a study by Curran et al. [48].

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**Table 4. Representative combination chemotherapy trials in advanced disease**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Setting</th>
<th>No. of patients</th>
<th>Overall response rate (%)</th>
<th>Complete response rate (%)</th>
<th>Median response (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin et al. [42]</td>
<td>PACPr</td>
<td>Stage III–IVA (induction)</td>
<td>13</td>
<td>92</td>
<td>23</td>
<td>–</td>
</tr>
<tr>
<td>Kim et al. [43]</td>
<td>PACPr</td>
<td>Stage III–IVB (induction)</td>
<td>22</td>
<td>77</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Loeher et al. [55]</td>
<td>PAC</td>
<td>Metastatic/recurrent</td>
<td>30 (1 thymic carcinoma)</td>
<td>50</td>
<td>10</td>
<td>11.8</td>
</tr>
<tr>
<td>Fornasiero et al. [56]</td>
<td>ADOC</td>
<td>Stage III–IV</td>
<td>37</td>
<td>92</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Loeher et al. [57]</td>
<td>VIP</td>
<td>Advanced thymic cancer</td>
<td>28</td>
<td>32</td>
<td>0</td>
<td>11.9</td>
</tr>
<tr>
<td>Giaccone et al. [58]</td>
<td>EP</td>
<td>Metastatic/recurrent</td>
<td>16</td>
<td>56</td>
<td>31</td>
<td>40.8</td>
</tr>
</tbody>
</table>

Abbreviations: ADOC, doxorubicin, cisplatin, vincristine, and cyclophosphamide; EP, cisplatin and etoposide; PAC, cisplatin, doxorubicin, and cyclophosphamide; PACPr, cisplatin, doxorubicin, cyclophosphamide, and prednisone; VIP, etoposide, ifosfamide, and cisplatin.
with metastatic or locally progressive recurrent disease [55]. Among 30 evaluable patients (29 thymomas, one thymic carcinoma), with a median of seven cycles of therapy, an overall response rate of 50% was observed (three complete responses and 12 partial responses). The median duration of response was 11.8 months, and the median survival time was 37.7 months. Durable responses have also been observed with doxorubicin, cisplatin, vincristine, and cyclophosphamide (ADOC), etoposide, ifosfamide, and cisplatin (VIP), and cisplatin and etoposide (EP) (Table 4) [56–58]. Ongoing trials include an Eastern Cooperative Oncology Group (ECOG) phase II trial investigating carboplatin and paclitaxel in advanced thymoma and thymic carcinoma.

Additional Therapies
Oxandrolone, in combination with prednisone, has been explored as a therapeutic option in thymoma based on the observation that thymomas highly express the somatostatin receptor on their surface and radiolabeled oxandrolone exhibits high specificity for thymoma compared with thymic hyperplasia and other benign thymic disorders [59, 60]. Complete clinical response in a patient with malignant thymoma and PRCA has been reported with oxandrolone and prednisone [61]. Based on these observations, a phase II trial was performed to assess the objective response rate, toxicity, and duration of response of oxandrolone alone or in combination with prednisone in 38 evaluable patients with advanced thymic cancer (32 thymoma, five thymic carcinoma, one thymic carcinoid) [62]. Patients received oxandrolone (0.5 mg s.c. three times a day) for a maximum of 1 year. If a patient exhibited a complete or partial response at 2 months, oxandrolone was continued alone. Stable disease at 2 months resulted in the addition of oral prednisone (0.6 mg/kg per day). Therapy was continued for 12 months. Two complete and 10 partial responses were observed, with an overall objective response rate of approximately 32%. Of note, all responses were observed in patients with thymoma. The progression-free survival duration for the combination of oxandrolone and prednisone was 9.2 months, compared with 2 months for oxandrolone alone (p = .039). The median survival time for patients with thymoma receiving the combination had not been reached and was 46.3 months for those receiving oxandrolone alone. These results suggest that objective responses can be obtained with oxandrolone alone or in combination with prednisone in patients with advanced disease.

Novel therapeutic strategies have additionally been explored. Case reports exist examining the role of transplant for treatment of invasive thymoma, and a clinical trial examining the role of umbilical cord transplantation in malignant thymoma is currently recruiting patients (http://www.clinicaltrials.gov) [63, 64]. Results of targeted therapies, specifically gefitinib, have been reported as well [65]. Twenty-six patients with metastatic or recurrent thymic malignancies (19 thymoma, seven thymic carcinoma) received 250 mg gefitinib daily, with therapy continued for a total of six cycles if there was no evidence of progressive disease after 2 months. One partial response of 14.8 months duration was obtained. Although disappointing, the strategy of incorporating novel therapeutics in the advanced setting is promising.

Summary
Thymoma is a rare neoplasm with a largely indolent growth pattern. Because of its potential for invasion and local recurrence, however, a multidisciplinary approach is recommended for the evaluation and treatment of these patients. Although responsive to both chemotherapy and radiation, the mainstay of treatment is surgical resection. Inoperable patients warrant a strategy of induction chemotherapy followed by a surgical reassessment post-therapy, and adjuvant radiation therapy is generally recommended, despite lacking prospective studies, for any evidence of invasive disease regardless of the degree of resection obtained. Durable responses can be obtained both in the metastatic and recurrent setting, and novel therapies are currently being explored.

Case Presentation Follow-Up

Case Presentation 1
The patient was referred to thoracic surgery where she underwent en bloc resection (total thymectomy). Pathology revealed a well-encapsulated 8.3-cm spindle-cell thymoma. Surgical margins were negative and there was no evidence of macroscopic or microscopic capsular invasion (Masaoka stage I). Given the low risk for recurrence for a completely resected stage I thymoma, no adjuvant therapy was recommended.

Case Presentation 2
The patient was presented at our multidisciplinary thoracic oncology conference. Disease recurrence appeared to be limited to the right anterolateral pleura. Referral to radiation oncology for consideration of intensity-modulated radiation therapy was recommended.

Acknowledgments
Special thanks to Dr. Jeffrey Crawford for critical review of the manuscript.

Disclosure of Potential Conflicts of Interest
The authors indicate no potential conflicts of interest.
REFERENCES


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