A 61-year-old man was referred to the thoracic oncology service of this hospital for management of a thymoma. He had been well until 6 weeks earlier, when he experienced the sudden onset of sharp left anterior chest pain, which was worse adjacent to the sternum and when he took a deep breath. He went to the emergency room of another hospital. Computed tomographic (CT) scanning of the chest performed with a pulmonary-embolism protocol revealed no evidence of pulmonary embolism. However, a lobulated, soft-tissue mass, 4 cm in diameter, was found in the left anterior mediastinum, adjacent to the main pulmonary artery and left main pulmonary artery and contiguous with the pericardium. There was no mediastinal or hilar lymphadenopathy, and the lungs were clear. He was referred to a thoracic surgeon at that hospital.

A whole-body positron-emission tomographic (PET) scan obtained 2 weeks after the onset of symptoms (Fig. 1) showed increased uptake of tracer in the area of the lesion, with no other areas of increased uptake. A bone scan was negative. The results of pulmonary-function testing were consistent with moderate mixed obstructive and restrictive disease, with a forced expiratory volume in 1 second of 1.96 (56% of the predicted value) and a forced vital capacity of 3.12 (59% of the predicted value). A bronchoscopic examination performed 1 month after the onset of symptoms showed no endobronchial lesions. Mediastinoscopy was performed, and examination of biopsy specimens of four mediastinal lymph nodes with frozen sections revealed no malignant tumor. A left anterior, mediastinal exploration with biopsy (Chamberlain procedure) was then performed; there was a poorly circumscribed mass in the aortopulmonary window that appeared to invade the pericardium. Biopsy specimens were obtained, and a diagnosis was made of a predominantly cortical, type B1 thymoma, according to the World Health Organization (WHO) criteria. Cytologic examination of specimens of left-lung washings were negative for tumor. The patient was referred to this hospital for further treatment.

His chest pain had resolved spontaneously, and he did not have cough, dyspnea, sputum production, fever, or muscle weakness. There was no history of myasthenia gravis, pure red-cell aplasia, or hypogammaglobulinemia. The patient was obese and had hypertension and hypercholesterolemia. He had undergone parathyroidectomy for hyperparathyroidism and had been treated for Lyme disease; the Guillain–Barré
syndrome had developed after a tetanus toxoid injection, and he had undergone neck irradiation for pertussis in childhood. He had smoked cigarettes for 25 years and had quit smoking 20 years earlier. He was a retired university professor, with no unusual occupational exposures, and he did not have an unusual travel history. His medications were lisinopril, simvastatin, and gabapentin.

On physical examination, the patient’s vital signs were normal. He had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 37. There was no jugular venous distention. There was no cervical or supraclavicular lymphadenopathy. The chest was clear on auscultation. There was no tenderness on palpation of the ribs or sternum. The remainder of the examination was normal.

A decision regarding management was made.

**Differential Diagnosis**

Dr. Jo-Anne O. Shepard: The initial examination, a CT study performed with intravenous contrast material (Fig. 1A and 1B), did not show a pulmonary embolism. A soft-tissue mass was identified in the left anterior mediastinum. It was noncalcified, with soft-tissue attenuation, and was somewhat lobulated in configuration. The mass was contiguous with the main pulmonary artery and the pericardium. There was no specific, direct evidence of vascular invasion, but the question of pericardial invasion was raised.

Whole-body PET (\(^{18}\)F-fluorodeoxyglucose [FDG]) scanning (Fig. 1C), performed shortly after the initial examination, showed a focus of FDG uptake in the anterior mediastinum that corresponded with the CT finding. The increased uptake on the PET scan suggested a malignant lesion.

The radiologic differential diagnosis at this point would include a thymic neoplasm, a lymphoma or a germ-cell neoplasm, and — potentially but less likely — a solitary focus of metastatic disease to the mediastinum. We did not see other sites of abnormal lymphadenopathy either on the CT scan or on the PET scan.

Dr. Cameron D. Wright: An anterior mediastinal mass was discovered incidentally while this patient was undergoing evaluation for acute chest pain. The relationship between the pain and the tumor that was eventually identified is not clear. The original investigation focused on possible lung cancer with hilar lymphadenopathy, despite the absence of an obvious lung lesion. Although in rare cases lung cancer presents in this manner, a careful review of the CT scan suggests that the mass is probably an anterior mediastinal lesion.
rather than lymphadenopathy. The mass is smooth in contour and homogeneous, and it does not look like a cluster of lymph nodes.

The most likely causes of an anterior mediastinal mass in a patient of this age are lymphoma and thymoma. Given the appearance of the mass on CT, the age of the patient, and the absence of symptoms, the most likely diagnosis is thymoma. My first choice for a diagnostic procedure in this situation would have been a CT-guided core needle biopsy; if this procedure had been nondiagnostic, I would have performed an anterior mediastinotomy with an incisional biopsy, which was the diagnostic procedure performed in this case.

Examination of the biopsy specimen showed that this tumor was a thymoma. Although thymomas are the most common mediastinal tumors, accounting for about 50% of all anterior mediastinal tumors, their overall incidence is very low, with only about 1.5 cases per million persons per year. The usual age at the time of diagnosis is the sixth decade. The sex distribution is equal. About one third to one half of the patients are symptomatic. Most symptoms are due to pressure from the tumor on surrounding structures or invasion of these structures, and include chest pain, dyspnea, cough, and the superior vena cava syndrome. Paraneoplastic syndromes, which are common, include myasthenia gravis, occurring in about one third of patients; hypogammaglobulinemia; and red-cell aplasia. Patients with thymomas are at increased risk for the development of another malignant tumor. This patient has no evidence of a paraneoplastic syndrome or another malignant condition and does not have symptoms related to the mass.

PATHOLOGICAL DISCUSSION

Dr. Robert P. Hasserjian: Multiple biopsy specimens were obtained from the mediastinal tumor and tissue from the ascending aorta, pulmonary artery, and pericardium. Examination of all the specimens showed a tumor composed predominantly of small lymphoid cells with the immunophenotype of cortical thymocytes (Fig. 2). Thymic epithelial cells were scattered throughout the tumor and were present in increased numbers within vaguely nodular areas that were histologically reminiscent of thymic medulla. These features are diagnostic of a thymoma.

Thymomas are neoplasms of thymic epithelial cells that vary greatly in both their morphologic features and their tendency to invade or recur. This histologic and biologic variability has resulted in controversy regarding their classification. The WHO recently proposed a classification system for thymoma based on the morphologic characteristics of the neoplastic epithelial cells and their relationship to the thymic lymphocytes (Table 1). In this case, the presence of numerous thymic T cells and pale areas recapitulating medullary differentiation were diagnostic of a type B1 thymoma. The diagnosis, classification, and staging of thymoma may be difficult with small biopsy samples, such as those that were obtained in this case. The presence of thymocytes can mimic either normal thymus or a lymphoblastic lymphoma. Classification can be inaccurate because thymomas are often heterogeneous, and diverse components may not have been sampled. A B1 thymoma such as this one may occur as a pure histologic type or it may be associated with areas of type A thymoma, in which case a diagnosis of type AB thymoma is made; AB thymomas are associated with a lower risk of invasion or recurrence than type B1 thymomas (Table 1). Less often, a B1 thymoma is seen with a B2 thymoma, which is a more aggressive tumor. In this case, because of the small biopsy samples, the presence of areas of type A or type B2 thymoma elsewhere in the tumor cannot be ruled out. Finally, the biopsy samples were too small to assess capsular invasion or invasion of adjacent structures, and the findings were thus inconclusive with regard to tumor stage. Four specimens of mediastinal lymph nodes were negative.

DISCUSSION OF MANAGEMENT

STAGING AND RESECTABILITY OF THYMOMA

Dr. Wright: My most important task as a thoracic surgeon assessing a patient with a thymoma was to determine whether the tumor was amenable to a complete resection and its likelihood of recurrence after surgery alone. Stage, WHO histologic type, tumor size, and status with regard to complete resection are independent predictors of the prognosis in thymoma.

The most commonly used staging system for thymoma is the postsurgical system devised by Masaoka in 1981 (Table 2). Unfortunately, it is difficult to assign a stage preoperatively because of the difficulty of assessing tumor invasion on
CT scans.\textsuperscript{15} When the tumor is small (<5 cm), is mostly surrounded by fat, and does not abut the lung, hilum, or great vessels, the surgeon can predict with confidence that a complete resection can be done. Extensive abutment of the pericardium or lung without a fat plane means that it is difficult to be sure that there is no microscopical invasion of these structures. The presence of symptoms is a good predictor of invasion and should be weighed in deciding on the probable stage of the tumor.\textsuperscript{16} In this case, the tumor is smaller than 5 cm in diameter, but the CT scan indicates that there may be invasion of the pericardium.

The WHO histologic type of thymoma can help predict resectability (Table 1).\textsuperscript{10-12} Type A thymomas are almost always noninvasive, so if this tumor were type A, I would be confident that it could be resected, regardless of its size. Both type A and type AB thymomas rarely recur and seldom require additional therapy after resection, even if focal invasion is present. Type B thymomas (B1, B2, and B3) are often invasive, and a B3 tumor, in particular, is likely to be at an advanced stage and unresectable. This patient's thymoma was a B1 tumor, which has an intermediate likelihood of invasion or recurrence.

Finally, the size of the tumor can help predict the likelihood that the tumor will be resectable and the chance of recurrence. A diameter larger than 8 cm is an independent predictor of recurrence.\textsuperscript{16} This patient's tumor is 4 cm in diameter, and tumors of this size are often resectable; however, the surgeon who performed the biopsies was convinced that it was invading the pericardium.

Stage I and II thymomas are almost always

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**Figure 2. Biopsy Specimens of Mediastinal Tumor.**

A low-magnification view (Panel A, hematoxylin and eosin) shows sheets of small lymphocytes with interspersed paler areas (arrow) resembling thymic medulla; the inset shows normal thymus and thymic medulla (arrows). On high magnification (Panel B, hematoxylin and eosin), large epithelial cells with delicate chromatin and small nucleoli (arrows) are scattered among the predominant population of small lymphocytes. Immunoperoxidase staining (Panels C and D) shows that the majority of the cells within the tumor are cortical thymocytes expressing terminal deoxynucleotidyl transferase (TdT), an immature lymphoid marker (Panel C); the neoplastic thymic epithelial cells are negative for TdT (Panel C, arrows) but express cytokeratin protein (Panel D, arrows).
completely resectable and cured with surgery alone, whereas stage III tumors may recur, most
commonly in the ipsilateral pleural space from droplet metastases (Table 2).

Thus, stage I and II lesions require no adjuvant therapy, whereas many stage III thymomas have positive mar-
gins and require postoperative therapy. I discussed the intraoperative findings in this patient with the referring surgeon; he thought that the thymoma invaded at least the pericardium and was thus a stage III tumor. Therefore, I was concerned that the tumor would not be completely resectable.

A decade ago, the standard treatment for thymoma was resection in all patients whose tumors appeared to be resectable on the basis of the preoperative evaluation; if the tumor proved to be invasive or could not be completely resected, radiotherapy was offered as an adjuvant postoperative treatment. This approach led to incomplete resection in many patients, and about one third of patients with stage III tumors, such as this one, had a recurrence. This observation, together with the favorable experience with induction chemotherapy for lung cancer, led many centers to recommend induction therapy before attempted resection of invasive thymomas, and my colleagues and I follow this approach at this hospital.

Although there are no randomized, controlled trials showing that induction therapy improves survival among patients with locally advanced thymomas, multiple case series have suggested an improvement in survival with induction therapy before surgery. This patient had a type B thymoma that was clinically estimated to be stage

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**Table 1. Histologic and Clinical Features of Thymomas According to the WHO Classification.**

<table>
<thead>
<tr>
<th>WHO Type</th>
<th>Epithelial Cells</th>
<th>Lymphocytes</th>
<th>Invasive Complete Resection</th>
<th>Average Stage</th>
<th>Recurrence</th>
<th>20-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Spindle-cell morphologic features, resembling medullary epithelial cells</td>
<td>Sparse; mature medullary thymocyte type</td>
<td>11%</td>
<td>100%</td>
<td>1.2</td>
<td>0%</td>
</tr>
<tr>
<td>AB</td>
<td>Mixed type A and type B features</td>
<td>Mixed type A and type B features</td>
<td>42%</td>
<td>99%</td>
<td>1.5</td>
<td>5%</td>
</tr>
<tr>
<td>B1</td>
<td>Sparse; both cortical and medullary type, recapitulating thymic architecture</td>
<td>Predominant; immature cortical thymocyte type, with areas of mature medullary thymocyte type</td>
<td>47%</td>
<td>95%</td>
<td>1.7</td>
<td>9%</td>
</tr>
<tr>
<td>B2</td>
<td>More numerous than in type B1; oval nuclei with prominent nucleoli and indistinct cytoplasm, resembling cortical epithelial cells</td>
<td>Predominant; immature cortical thymocyte type</td>
<td>69%</td>
<td>91%</td>
<td>2.3</td>
<td>18%</td>
</tr>
<tr>
<td>B3</td>
<td>Predominant; oval, often grooved nuclei and clear cytoplasm with distinct cell borders; cytologically atypical</td>
<td>Sparse; immature cortical thymocyte type</td>
<td>85%</td>
<td>92%</td>
<td>2.5</td>
<td>29%</td>
</tr>
</tbody>
</table>

* The information is from Marx et al. and Okumura et al.

**Table 2. The Masaoka Staging System and Results of Thymoma Treatment in 1320 Patients.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Complete Resection</th>
<th>Recurrence</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Completely encapsulated tumor</td>
<td>100%</td>
<td>1%</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
<td>Tumor that invades adjacent thymus, mediastinal fat, or mediastinal pleura</td>
<td>100%</td>
<td>4%</td>
<td>98%</td>
</tr>
<tr>
<td>III</td>
<td>Tumor that invades surrounding structures such as lung, pericardium, or great vessels</td>
<td>85%</td>
<td>28%</td>
<td>89%</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor with pleural or pericardial metastases</td>
<td>42%</td>
<td>34%</td>
<td>71%</td>
</tr>
<tr>
<td>IVB</td>
<td>Tumor with lymphogenous or hematogenous metastases</td>
<td>NA</td>
<td>34%</td>
<td>52%</td>
</tr>
</tbody>
</table>

* The information is from Kondo and Monden. NA denotes not applicable.
II because of pericardial invasion, so I recommended induction therapy and referred him to the medical oncology department.

**INDUCTION CHEMOTHERAPY FOR STAGE III THYMOMA**

Dr. Panos Fidias: In this patient with stage III thymoma, consideration of induction chemotherapy was based on experience with unresectable thymomas. The administration of corticosteroids alone may lead to a response, and corticosteroids in combination with octreotide are associated with response rates in the range of 30% among patients with unresectable thymomas. Combination chemotherapy in a patient with advanced, unresectable thymoma usually involves cisplatin-based regimens; however, responses have been reported with other regimens, such as cyclophosphamide, doxorubicin, and vincristine (CAV) or CAV with the addition of prednisone, with or without bleomycin. Typically, responses are seen in 30 to 90% of patients, and the median survival ranges from 2 to 4 years.

More recently, studies evaluating systemic treatment for locally advanced tumors that may not be completely resectable have shown that induction therapy with a combination of cyclophosphamide, doxorubicin administered by means of continuous infusion, cisplatin, and prednisone or cisplatin and etoposide with either preoperative or postoperative radiotherapy resulted in high overall response rates, with improved tumor resectability and progression-free survival.

On the basis of these studies, we recommended preoperative chemotherapy with two cycles of cisplatin (33 mg per square meter of body-surface area on days 1, 2, and 3) and etoposide (100 mg per square meter on days 1, 2, and 3), and we asked Dr. Choi from the radiation oncology department to consider concomitant radiotherapy. We planned to administer two additional cycles of the same drugs after the surgical removal of the tumor.

**PREOPERATIVE RADIOTHERAPY IN STAGE III THYMOMA**

Dr. Noah C.H. Choi: The conventional approach of surgery and postoperative radiotherapy for patients with stage III thymoma has resulted in a 5-year survival rate of about 60%, without noticeable improvement over the past 20 years. Even after postoperative radiotherapy, patients with incomplete resection have a 5-year survival rate of 20 to 40%; 50% of the recurrences are in the pleural cavity. However, radiotherapy with or without chemotherapy results in 5-year survival rates of 30 to 50% for patients with inoperable thymomas, indicating that some tumors can be controlled by these treatment approaches. Furthermore, a study has shown that patients with marginally resectable stage III thymomas who received radiotherapy preoperatively had improved recurrence-free and overall survival as compared with those who received radiotherapy after incomplete resection. These findings suggest that preoperative radiotherapy or chemoradiotherapy may increase survival by improving the rate of complete resection and reducing local and pleural recurrences.

Since this patient’s tumor was close to the heart, the esophagus, and the spinal cord, we used intensity-modulated radiotherapy (see Fig. 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). With this technique, we can plan the radiation dose to fit the target volume and spare the adjacent normal organs and tissues better than we can with standard three-dimensional radiotherapy. In this patient, intensity-modulated radiotherapy consisted of a total dose of 45 Gy administered in 25 fractions over a period of 5 weeks. The radiotherapy was given concomitantly with chemotherapy.

**SURGICAL MANAGEMENT OF THYMOMA**

Dr. Shepard: After the patient had received chemotherapy and radiotherapy, repeated CT scanning with contrast material (Fig. 3) and whole-body PET–CT scanning were performed. The CT scan showed a marked decrease in the size of the mass, and there was more fat interspersed between the mass and pericardium as compared with previous examinations. The PET–CT scan showed no evidence of abnormal FDG uptake.

Dr. Wright: The patient had an excellent response to induction treatment, with the PET scan showing resolution of the hypermetabolic focus and the CT scan showing a marked reduction in the size of the tumor. Although complete resolution of FDG uptake on a PET scan suggests an absence of gross viable tumor, it does not necessarily indicate a complete absence of morphologically viable tumor cells. Extrapolation from other thoracic cancers (esophageal and lung cancers) suggests that normal uptake on PET scanning after induction therapy indicates a favorable prognosis.
since the radiographic response is a rather poor
discriminator of the response to therapy, most tho-
racic cancers that are treated with induction ther-
apy are subsequently resected, regardless of the
degree of radiographic response. I recommended
that this patient undergo a mediastinotomy and re-
section of the residual mass and thymus gland.

At surgery, I found a heavily scarred, residual
mass adherent to the pericardium, projecting into
the left pleural space and densely adherent to the
left phrenic nerve. I removed all mediastinal fatty
tissue, encompassing the entire thymus gland,
and I resected the pericardium underneath the
thymus gland and around the mass. There was
no evidence of tumor invasion through the peri-
cardium. I did not want to resect the left phrenic
nerve, since the patient had preexisting lung dis-
ease and I was concerned about impaired lung
function if the diaphragm was paralyzed. I dissect-
ed the phrenic nerve from the edge of the residu-
ial mass, completed the resection, marked the
phrenic-nerve margins with metallic clips in case
we thought more radiotherapy would be benefi-
cial, and oriented the specimen for the patholo-
gist. A frozen section of the area close to the
phrenic nerve was negative for tumor. The patient
had an uneventful recovery and was discharged
to his home after 5 days in the hospital.

PATHOLOGICAL FINDINGS
Dr. Hasserjian: The resection specimen contained a
3.0-cm, irregular, firm area in the left lobe of the
thymus, adjacent to the lateral resection margin,
which contained residual thymoma. On microscop-
ical examination, a 3.0-mm area resembled the
tumor from the previous biopsy of the thymoma
(Fig. 4A). However, most of the residual tumor
consisted of sheets of epithelial cells in a fibrotic
background (Fig. 4B). Histologic changes in thymoma after therapy are not well documented in the literature, although tumor necrosis and reduced proliferation of neoplastic cells were reported in one study. In the current case, most of the residual tumor did not resemble any particular thymoma type and probably represented involutional changes in the tumor that were induced by the chemotherapy and radiotherapy. The tumor extended focally to the lateral resection margin on permanent sections; it did not invade the attached pericardium.

**Dr. Wright:** The patient received two additional cycles of chemotherapy and is well 4 years after the diagnosis, with no evidence of recurrent disease on serial CT scans. Long-term follow-up is required for patients with thymomas, since recurrences are routinely seen more than 10 years after treatment.

**Dr. Harris:** Was additional radiotherapy considered because of the positive margin?

**Dr. Choi:** We considered a postoperative booster dose of radiation to the tumor-bed region where the resection margin was positive for microscopical residual disease. However, the patient remained short of breath for several months after surgery. Thus, no additional radiotherapy was given.

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**ANATOMICAL DIAGNOSIS**

Thymoma, WHO type B1, with individual changes after preoperative chemoradiation.

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**REFERENCES**


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