e12 Thymoma

Dan L. Longo

The thymus is derived from the third and fourth pharyngeal pouches and is located in the anterior mediastinum. The thymus is composed of epithelial and stromal cells derived from the pharyngeal pouch and lymphoid precursors derived from mesodermal cells. It is the site to which bone marrow precursors that are committed to differentiate into T cells migrate to complete their differentiation. Like many organs, it is organized into functional regions—in this case, the cortex and the medulla. The cortex of the thymus contains ~85% of the lymphoid cells and the medulla ~15%. It appears that the primitive bone marrow progenitors enter the thymus at the corticomedullary junction and migrate first through the cortex toward the periphery of the gland and then toward the medulla as they mature. Medullary thymocytes have a phenotype that cannot readily be distinguished from mature peripheral blood and lymph node T cells.

Several things can go wrong with the thymus, but thymic abnormalities are very rare. If the thymus does not develop properly, serious deficiencies in T cell development ensue and severe immunodeficiency is seen (e.g., DiGeorge syndrome, Chap. 310). If a lymphoid cell within the thymus becomes neoplastic, the disease that develops is a lymphoma. The majority of lymphoid tumors that develop in the thymus are derived from the precursor T cells, and the tumor is a precursor T cell lymphoblastic lymphoma (Chap. 105). Rare B cells exist in the thymus, and when these become neoplastic, the tumor is a mediastinal (thymic) B cell lymphoma (Chap. 105). Germ cell tumors and carcinoid tumors may occasionally arise in the thymus. If the epithelial cells of the thymus become neoplastic, the tumor that develops is a *thymoma*.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Thymoma is the most common cause of an anterior mediastinal mass in adults, accounting for ~40% of all mediastinal masses. The other major causes of anterior mediastinal mass are lymphomas, germ cell tumors, and substernal thyroid tumors. Carcinoid tumors, lipomas, and thymic cysts may also produce radiographic masses. Thymomas are most common in the fifth and sixth decades, are uncommon in children, and are distributed evenly between men and women.

About 40–50% of patients are asymptomatic; masses are detected incidentally on routine chest radiographs. When symptomatic, patients may have cough, chest pain, dyspnea, fever, wheezing, fatigue, weight loss, night sweats, or anorexia. Occasionally, thymomas may obstruct the superior vena cava. About 40% of patients with thymoma have another systemic autoimmune illness related to the thymoma. About 30% of patients with thymoma have myasthenia gravis, 5–8% have pure red cell aplasia, and ~5% have hypogammaglobulinemia. Among patients with myasthenia gravis, ~10–15% have a thymoma. Thymoma more rarely may be associated with polymyositis, systemic lupus erythematosus, thyroiditis, Sjögren's syndrome, ulcerative colitis, pernicious anemia, Addison's disease, scleroderma, and panhypopituitarism. In one series, 70% of patients with thymoma were found to have another systemic illness (Souadjian et al, 1974).

DIAGNOSIS AND STAGING

Once a mediastinal mass is detected, a surgical procedure is required for definitive diagnosis. An initial mediastinoscopy or limited thoracotomy can be undertaken to get sufficient tissue to make an accurate diagnosis. Fine-needle aspiration is poor at distinguishing between lymphomas and thymomas but is more reliable in diagnosing germ cell tumors and metastatic carcinoma. Thymomas and lymphomas require sufficient tissue to examine the tumor architecture to assure an accurate diagnosis and obtain prognostic information.

Once a diagnosis of thymoma is defined, subsequent staging generally occurs at surgery. However, chest CT scans can assess local invasiveness in some instances. MRI has a defined role in the staging of posterior mediastinal tumors, but it is not yet clear that it adds important information to the CT scan in anterior mediastinal tumors. Somatostatin receptor imaging with indium-labeled somatostatin analogues may be of value (Lin et al, 1999). If invasion is not distinguished by noninvasive testing, an effort to resect the entire tumor should be undertaken. If invasion is present, neoadjuvant chemotherapy may be warranted before surgery (see "Treatment," below).

TABLE e12-1 MASAOKA STAGING SYSTEM FOR THYMOMAS

Stage	Diagnostic Criteria
I	Macroscopically and microscopically completely encapsulated; no invasion through capsule
II	
IIA	Microscopic invasion outside of the capsule
IIB	Macroscopic invasion into surrounding fat or grossly adherent to pleura or pericardium
III	
IIIA	Macroscopic invasion into neighboring organs, pericardium, or pleura but not the great vessels
IIIB	Macroscopic invasion into neighboring organs that includes great vessels
IV	
IVA	Pleural or pericardial dissemination
IVB	Lymphatic or hematogenous metastases

Stage	Stage Distribution, %	5-Year Survival, %	10-Year Survival, %
I	65	95–100	86–100
II	25	70–100	5–100
III	5	50–70	47–60
IV	5	11–50	0–11

Source: From A Masaoka et al: Cancer 48:2485, 1981.

Some 90% of thymomas are in the anterior mediastinum, but some may be in other mediastinal sites or even the neck, based on aberrant migration of the developing thymic enlage.

The staging system for thymoma was developed by Masaoka and colleagues (Table e12-1). It is an anatomic system in which the stage is increased based on the degree of invasiveness. The 5-year survival of patients in the various stages is as follows: stage I, 96%; stage II, 86%; stage III, 69%; stage IV, 50%. The French Study Group on Thymic Tumors (GETT; Cowen et al, 1998) has proposed modifications to the Masaoka scheme based upon the degree of surgical removal because the extent of surgery has been noted to be a prognostic indicator. In their system, stage I tumors are divided into A and B based on whether the surgeon suspects adhesions to adjacent structures; stage III tumors are divided into A and B based upon whether disease was subtotally resected or only biopsied. The concurrence between the two systems is high.

PATHOLOGY AND ETIOLOGY

Thymomas are epithelial tumors and all of them have malignant potential. It is not worthwhile to try to divide them into benign and malignant forms; the key prognostic feature is whether they are noninvasive or invasive. About 65% of thymomas are encapsulated and noninvasive and about 35% are invasive. They may have a variable percentage of lymphocytes within the tumor, but genetic studies suggest that the lymphocytes are benign polyclonal cells. The epithelial component of the tumor may consist primarily of round or oval cells derived mainly from the cortex or spindle-shaped cells derived mainly from the medulla or combinations thereof (Table e12-2). Cytologic features are not reliable predictors of biological behavior. About 90% of A, AB, and B1 tumors are localized. A very small number of patients have aggressive histology features characteristic of carcinomas. Thymic carcinomas are invasive and carry a poor prognosis.

The genetic lesions in thymomas are not well characterized. Some data suggest that Epstein-Barr virus may be associated with thymomas (Dimery et al, 1988). Some tumors overexpress the p21 *ras* gene product. However, molecular pathogenesis remains undefined. A thymoma susceptibility locus has been defined on *rat* chromosome 7, but the re-

TABLE e12-2 WHO HISTOLOGIC CLASSIFICATION OF THYMUS TUMORS[a]

Type	Histologic Description
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma
C	Thymic carcinoma

Type	Distribution, %	Prognosis (10-year disease-free survival), %
A	8	100
AB	17	100
B1	27	83
B2	8	83
B3	12	36
C	28	28

[a]WHO, World Health Organization.

lationship between this gene locus, termed *Tsr1*, and human thymoma has not yet been examined.

℞ THYMOMA

Treatment is determined by the stage of disease. For patients with encapsulated tumors and stage I disease, complete resection is sufficient to cure 96% of patients. For patients with stage II disease, complete resection is usually followed by 30–60 Gy of postoperative radiation therapy to the site of the primary tumor. For patients with stage III and IV disease, the use of neoadjuvant chemotherapy followed by radical surgery, radiation therapy, and additional consolidation chemotherapy has been associated with excellent survival in a small group of patients so treated (Shin et al, 1998). Induction chemotherapy consisted of cyclophosphamide 500 mg/m^2 on day 1; continuous-infusion doxorubicin, 20 mg/m^2 per day on days 1–3 (total 60 mg/m^2); cisplatin, 30 mg/m^2 per day on days 1–3 (total 90 mg/m^2); and prednisone, 100 mg/d on days 1–5. Three cycles were given in 3- to 4-week intervals. Of 12 patients treated with this regimen, 3 had complete responses, 8 had partial responses, and 1 had a minor response. These patients then underwent surgical resection; tumor was completely resected in nine and incompletely resected in two patients (one patient refused surgery and received radiation therapy only). After surgery, all patients received radiation therapy (50–60 Gy) and three additional courses of chemotherapy at 80% of the doses used for neoadjuvant therapy. At a median follow-up of 43 months, 10 of the 12 patients were free of disease, and the 2 patients who had local recurrence remain alive with disease. Survival at 7 years is 100%.

This multimodality approach appears to be superior to the use of surgery followed by radiation therapy alone, which produces a 5-year survival of ≤50% in patients with advanced-stage disease.

Some thymic carcinomas express *c-kit*, and one patient whose *c-kit* locus was mutated responded dramatically to imatanib. Many thymomas express epidermal growth factor receptors, but the antibodies to the receptor and kinase inhibitors that block its action have not been systematically evaluated. Octreotide plus prednisone produces responses in about one-third of patients.

INFLUENCE OF THYMECTOMY ON THE COURSE OF ACCOMPANYING DISEASES

Patients with myasthenia gravis have a high incidence of thymic abnormalities (~80%) but overt thymoma is present in only ~10–15% of patients with myasthenia gravis. It is thought that the thymus plays a role in breaking self-tolerance and generating T cells that recognize the acetylcholine receptor as a foreign antigen. Although patients with thymoma and myasthenia gravis are less likely to have a remission in the myasthenia as a consequence of thymectomy than are patients with thymic abnormalities other than thymoma, the course of myasthenia gravis is not significantly different in patients with or without thymoma (Bril et al, 1998). Thymectomy produces at least some symptomatic improvement in ~65% of patients with myasthenia gravis.

About 30–50% of patients with pure red cell aplasia have a thymoma. Thymectomy results in the resolution of pure red cell aplasia in ~30% of patients. About 10% of patients with hypogammaglobulinemia have a thymoma, but hypogammaglobulinemia rarely responds to thymectomy.

FURTHER READINGS

Bril V et al: The long-term clinical outcome of myasthenia gravis in patients with thymoma. Neurology 51:1198, 1998 [PMID: 9781560]

Cowen D et al: Natural history and treatment of malignant thymoma. Oncology 12:1001, 1998 [PMID: 9684271]

Dimery IW et al: Association of Epstein-Barr virus with lymphoepithelioma of the thymus. Cancer 61:2475, 1998 [PMID: 2835144]

Giaccone G: Treatment of malignant thymoma. Curr Opin Oncol 17:140, 2005 [PMID: 15725919]

Lin K et al: Somatostatin receptor scintigraphy and somatostatin therapy in the evaluation and treatment of malignant thymoma. Clin Nucl Med 24:24, 1999 [PMID: 9890489]

Petrie HT: Cell migration and the control of post-natal T-cell lymphopoiesis in the thymus. Nat Rev Immunol 3:859, 2003 [PMID: 14668802]

Shin DM et al: A multidisciplinary approach to therapy for unresectable malignant thymoma. Ann Intern Med 129:100, 1998 [PMID: 9669967]

Souadjian JV et al: The spectrum of diseases associated with thymoma. Arch Intern Med 134:374, 1974 [PMID: 4602050]

Wright CD: Management of thymomas. Crit Rev Oncol Hematol 64, 2007 [PMID: 17570676]