CHAPTER e20 Thymoma

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The thymus is derived from the third and fourth pharyngeal pouches and is located in the anterior mediastinum. It 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 contains ~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 be distinguished readily from that of 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. 316). 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. 110). Rare B cells exist in the thymus, and when they become neoplastic, the tumor is a mediastinal (thymic) B cell lymphoma (Chap. 110). Hodgkin's disease, particularly the nodular sclerosing subtype, often involves the anterior mediastinum. Extranodal marginal zone (MALT) lymphomas have been reported to involve the thymus in the setting of Sjögren's syndrome or other autoimmune disorders, and the lymphoma cells often express IgA instead of IgM on their surface. Castleman's disease can involve the thymus. Germ cell tumors and carcinoid tumors occasionally may 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 masses are lymphomas, germ cell tumors, and substernal thyroid tumors. Carcinoid tumors, lipomas, and thymic cysts also may produce radiographic masses. After combination chemotherapy for another malignancy, teenagers and young adults may develop a rebound thymic hyperplasia in the first few months after treatment. Granulomatous inflammatory diseases (tuberculosis, sarcoidosis) can produce thymic enlargement. 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. Thymoma with hypogammaglobulinemia also is called Good's syndrome. 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.

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 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. 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 "Approach to Treatment," below).

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 e20-1). It is an anatomic system in which the stage is increased on the basis of 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) has proposed modifications to the Masaoka scheme based on 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 on the basis of whether the surgeon suspects adhesions to adjacent structures; stage III tumors are divided into A and B based on 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 of the two types (Table e20-2). Cytologic features are not reliable predictors of

TABLE e20-1 Masaoka Staging System for Thymomas

Stage	Diagnostic Criteria
I	Macroscopically and microscopically completely encapsulated; no invasion through capsule
II	
IIA	Microscopic invasion outside 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 great vessels
IIIB	Macroscopic invasion into neighboring organs that includes great vessels
IV	
IVA	Pleural or pericardial dissemination
IVB	Lymphatic or hematogenous metastases

	Stage Distribution, %	5-Year Survival, %	10-Year Survival, %
I	36	95–100	86–100
II	26	70–100	50–100
III	22	68–89	47–60
IV	10	47–69	0–11

Source: From A Masaoka et al: Cancer 48:2485, 1981. Updated from S Tomaszek et al: Ann Thorac Surg 87:1973, 2009, and CB Falkson et al: J Thorac Oncol 4:911, 2009.

TABLE e20-2 World Health Organization (WHO) Histologic Classification of Thymus Tumors

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	26	90–100
B1	15	78–94
B2	28	83
B3	15	36
C	8	0–35

Source: From S Tomaszek et al: Ann Thorac Surg 87:1973, 2009.

biologic 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 have a poor prognosis.

The genetic lesions in thymomas are not well characterized. Some data suggest that Epstein-Barr virus may be associated with thymomas. 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 relationship between this gene locus, termed *Tsr1*, and human thymoma has not been examined.

TREATMENT 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 may be followed by 30–60 Gy of postoperative radiation therapy to the site of the primary tumor. However, the value of radiation therapy in this setting has not been established. The main predictors of long-term survival are Masaoka stage and completeness of resection. For patients with stage III and IV disease, the use of neoadjuvant chemotherapy followed by radical surgery, with or without additional radiation therapy, and additional consolidation chemotherapy has been associated with excellent survival. Chemotherapy regimens that are most effective generally include a platinum compound (either cisplatin or carboplatin) and an anthracycline. Addition of cyclophosphamide, vincristine, and prednisone seems to improve response rates. Response rates of 50–93% have been reported in series of patients each of which involved fewer than 40 patients. A single most effective regimen has not been defined. If surgery after neoadjuvant chemotherapy fails to produce a complete resection of residual disease, radiation therapy (50–60 Gy) may help reduce recurrence rates.

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 imatinib. Many thymomas express epidermal growth factor receptors, but the antibodies to the receptor and the kinase inhibitors that block its action have not been evaluated systematically. 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.

Thymectomy produces at least some symptomatic improvement in ~65% of patients with myasthenia gravis. In one large series, thymoma patients with myasthenia gravis had a better long-term survival from thymoma resection than did those without 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

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