Thoracic and Cardiovascular Surgery

Surgical Treatment of Thymic Tumors

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Thymoma is a rare neoplasm usually with an indolent growth pattern; however, local invasion and/or metastases may occur. The association with several paraneoplastic syndromes, especially myasthenia gravis, makes thymoma an interesting biologic tumor model. Surgery has been the standard of care for early stage disease with high cure rates anticipated. Multimodality therapy can result in long-term disease-free survival for patients presenting with locally advanced disease.
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Thymomas represent the most common mediastinal neoplasm as well as the most common anterior mediastinal compartment neoplasm, constituting about 20% and 50% of all mediastinal and anterior compartment tumors occurring in the adult population, respectively. However, the overall incidence of thymoma is rare, with 0.15 cases per 100,000, based on data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program.[1] Thymoma is an epithelial tumor generally considered to have an indolent growth pattern but malignant nonetheless because of potential for local invasion, pleural dissemination, and even systemic metastases. Most patients are between the age of 40 and 60 years at the time of diagnosis with an equal gender distribution. Approximately one-third of patients with localized disease at presentation are symptomatic, most commonly reporting cough or vague chest discomfort. With increasing use of routine CT screening, one would anticipate that a higher percentage of patients will present with asymptomatic disease. Patients demonstrating either locally advanced or disseminated thymoma at the time of presentation are usually symptomatic with significant chest pain, shortness of breath from lung involvement, phrenic nerve paralysis, pleural effusions, and/or SVC syndrome.

Of unique interest, several immune disorders have been associated with thymoma. Abnormal regulation of lymphocytes within the thymus gland can result in autoimmunity and/or immunodeficiency. Autoimmunity may also be caused by cross immunity of antigens in other tissues with thymoma associated antigens. As a result, several end organs may be affected and more than one immunologic disorder may be present in any given patient diagnosed with a thymoma. Myasthenia gravis is the most common autoimmune disease associated with thymoma. Approximately 30% to 65% of patients with thymoma have been diagnosed with myasthenia gravis in reported series.[2,3] Conversely, only 10% to 15% of patients with myasthenia gravis will have a thymoma. Patients with thymoma associated myasthenia gravis can produce autoantibodies to a variety of neuromuscular antigens, particularly the acetylcholine receptor and titin, a striated muscle antigen.[4,5] Up to 28% of thymoma patients will present with an immune disorder other than myasthenia gravis. The most common include pure red cell aplasia, lupus erythematosus, and hypogammaglobulinemia.[2,3]

Diagnosis

Patients presenting with the commonly associated diseases such as myasthenia gravis, red blood cell aplasia, or hypogammaglobulinemia should prompt investigation with a screening chest CT scan to rule out the presence of an asymptomatic thymoma. Conversely, symptoms which may be consistent with myasthenia gravis such as easy fatigability, muscular weakness, diplopia, ptosis, and dysarthria, should be elicited from any patient presenting with a mass in the anterior mediastinal compartment. Neurologic consultation should be considered if there is suspicion of myasthenia, particularly for any patient being evaluated for diagnostic and/or therapeutic surgical intervention, as severe respiratory morbidity can be minimized with appropriate perioperative management.[6-8]

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Chest CT scanning with intravenous contrast is the radiographic examination of choice for evaluation of all mediastinal masses in the anterior compartment. CT not only precisely defines size, density characteristics, and relationship to surrounding intrathoracic organs such as the great vessels, lungs, pericardium, and heart, but also the presence of pleural parietal pleural deposits or so called "droplet metastases" most frequently found in the posterior basilar pleural space and diaphragm. As this tendency to metastasize in the posterior basilar pleural space is rather unique to thymomas, the radiographic presence of both an anterior compartment mass and "droplet" metastases is highly suggestive of the diagnosis. In general, the differential diagnoses of patients presenting with a mass in the anterior mediastinal compartment are typically initially guided by patient's age, gender, associated symptoms, and CT appearance. Malignant germ cell tumors occur primarily in young adult males and can essentially be ruled out by measuring the serum tumor marker levels of alpha fetoprotein and the beta subunit of human chorionic gonadotropin.[9] Thyroid lesions involving the anterior mediastinal compartment are readily identified on CT scan as contiguous with the thyroid gland. Iodine^{131} nuclear medicine scans can be utilized to confirm a thyroid origin in rare cases where CT scanning is equivocal.

The two main differential diagnoses of most anterior compartment masses are therefore lymphoma and thymoma. In general, thymoma patients are older as compared with patients presenting with lymphoma originating in the anterior mediastinal compartment. Constitutional symptoms such as night sweats, fever, weight loss, and malaise are more consistent with lymphomas. Physical examination including careful palpation of lymph bearing areas such as the neck, axillae, and groins for adenopathy amenable to excisional biopsy, which might establish a diagnosis of lymphoma, is indicated. Anterior mediastinal masses that are associated with surrounding lymphadenopathy are usually lymphomas and should be biopsied rather than excised for diagnosis. A small anterior mediastinal compartment mass in a patient with a history of an associated immune disorder has a high probability of representing a thymoma. In general, we believe that wide surgical excision including enbloc thymectomy without biopsy is justified for both diagnostic and likely therapeutic purposes in patients with small anterior mediastinal masses that are clinically thought to be thymomas. The role of PET scan for thymoma is currently being evaluated. While not considered useful to differentiate thymoma from lymphoma, PET with 2-deoxy-2-[^{18}F] fluoro-D-glucose tracer can demonstrate hypermetabolic activity in pleural based masses identified on CT scan, which would be highly suggestive of metastatic thymoma.[10] PET can also be used to ascertain response to nonoperative therapy.

Following initial clinical and CT scan evaluation, biopsy of the anterior compartment mass may be indicated when lymphoma is suspected or a locally advanced thymoma is suspected. The least invasive technique is CT-guided FNA. Cytokeratin staining is a useful diagnostic marker for epithelial type cells in this regard.[11] It must be emphasized however that cytology not only lacks sensitivity, but also can be misleading with respect to differentiating thymomas and lymphomas.[12] Moreover, a substantial tissue sample for genetic marker studies including flow cytometry is considered optimal before treatment for lymphoma. Accordingly, we have become less reliant on CT-guided FNA cytology for diagnosis. In our experience, CT-guided core needle biopsy can usually be safely performed for most larger masses in the anterior compartment, particularly if a large bore needle can be passed into the mass without traversing lung parenchyma. Core needle biopsies allow histologic examination of the tumor, and immunohistochemical stains can be performed to allow accurate diagnosis. If core needle biopsy is not possible, then two surgical options exist for further diagnostic evaluation. For larger and/or invasive masses, we consider anterior (or "Chamberlain") mediastinotomy the next diagnostic procedure of choice. The Chamberlain procedure may be performed on either side and at any level which best provides the access to any given anterior mediastinal tumor. Standard cervical mediastinoscopy does not provide access to the anterior compartment, and therefore should be avoided unless significant paratracheal lymphadenopathy suspicious of metastatic disease is present. Video-assisted thoracic surgery (VATS) does provide excellent exposure to the anterior compartment for biopsy purposes using minimally invasive technology; however, the pleural space is traversed and if thymoma is a diagnostic possibility, pleural space seeding could theoretically occur during VATS biopsy efforts. For small lobulated solid masses identified in the anterior mediastinal compartment not amenable to core needle biopsy, several diagnostic options exist. Although open Chamberlain or VATS biopsy could be performed in otherwise healthy patients, we would advocate complete surgical excision including total thymectomy as a reasonable approach for both diagnostic and therapeutic purposes. Most small lobulated masses in this age group will represent an early stage thymoma.

Staging

Many histological classifications have been described for thymoma and thymic neoplasms in general. Most recently, the World Health Organization reached a consensus on histologic classification based on both morphology and lymphocyte to epithelial cell ratio.[13]

In 1981, Masaoka initially proposed an anatomic classification based on the presence or absence of gross or microscopic invasion of the capsule and the presence or absence of metastases.[14] This classification was subsequently revised in 1994 (Table 1).[15] Several studies have attempted to correlate morphologic staging systems with tumor invasion and prognosis.[16,17] It appears that medullary (WHO A) and mixed histology (WHO AB) tumors are typically not invasive and therefore usually correspond to Masaoka Stages I and II. Conversely, cortical (WHO B1, B2, or B3) thymomas are more invasive and occur more commonly as Stage III and IV lesions. The Masaoka staging system remains as the most widely accepted staging system on which current management recommendations are based.