Approach to the Diagnosis and Staging of Mediastinal Masses*
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Improvements in cytologic techniques have made needle biopsy much more helpful in diagnosing mediastinal masses. We have added thoracoscopy to the surgical armamentarium. Tumor markers facilitate accurate diagnosis. In the field of imaging, cysts can now be identified almost certainly and aspirated. Magnetic resonance imaging has changed the workup of patients with posterior mediastinal masses. Staging investigations should be based on the type of tumor and the likelihood of spread. (Chest 1993; 103:328S-30S)

In recent years, several developments have facilitated the diagnosis and staging of mediastinal masses. Improvements in cytologic techniques have made needle biopsy much more helpful in diagnosis. We have added thoracoscopy to the surgical armamentarium, thus changing the surgical approach to many mediastinal masses. Tumor markers, both serum and tissue, simplify accurate diagnosis. In germ cell tumors, serum markers can be used to make a definitive diagnosis, even without tissue. Imaging permits almost certain identification of cysts and can even guide their aspiration. Magnetic resonance imaging (MRI) has changed the workup of patients with posterior mediastinal masses.

Each compartment of the mediastinum (anterior, visceral, and paravertebral) has its own most common lesions. Knowing the location of the mass and the age, sex, and symptoms of the patient can help establish a preliminary diagnosis to guide further investigation.

For instance, a young man with an anterior mediastinal mass may have a lymphoma, thymoma, or germ cell tumor. First, draw blood to investigate for tumor markers: α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and placental alkaline phosphatase. These have great accuracy in malignant germ cell tumors, and the pattern they reveal can indicate the diagnosis. A patient with tumor markers can be treated appropriately with chemotherapy or radiotherapy, even in the absence of a tissue diagnosis. If tumor markers are absent, fine needle aspiration (FNA) should help make the diagnosis.

Other patients with clinically benign anterior mediastinal masses, especially those involving the thyroid or thymus, may be scheduled for surgical excision without prior biopsy. Asymptomatic thyroid masses need not be removed. Clinically malignant lesions should be diagnosed with FNA. If FNA does not yield the diagnosis, or if you strongly suspect Hodgkin’s disease, anterior mediastinotomy may be the next step. Evaluate the airway carefully by reviewing symptoms and checking for airway compromise before choosing a method of anesthesia.

In the visceral compartment, which most likely contains foregut cysts (bronchogenic and esophageal), lymphoma, and pleuropericardial cysts, cystic lesions may be excised without prior biopsy. Appropriate approaches include mediastinoscopy, thoracoscopy, and thoracotomy. For lesions in the anterior cardiophrenic angle (usually pleuropericardial cysts), FNA will both diagnose and treat the problem. The superior and midportions of the visceral compartment usually contain either goiter or lymphoid tissue. If FNA fails to indicate a diagnosis, consider biopsy of paratracheal nodes by mediastinoscopy and other nodes by the most appropriate surgical approach, bearing in mind the potential complications of general anesthesia.

The paravertebral sulcus mass usually represents a neurogenic tumor. All infants and children with paravertebral masses should be tested for excessive epinephrine and norepinephrine levels (for neuroblastoma and pheochromocytoma), and the mass then excised. Children and adults require a pre-excision biopsy only rarely.

**Diagnosis**

**Fine Needle Aspiration Biopsy**

Successful diagnosis by FNA with radiologic guidance (most commonly computed tomography [CT]) requires close communication among the clinician, radiologist, and pathologist. A pathologist typically can assign an FNA of a mediastinal mass to one of the following categories: thymus, lymph node, thyroid, seminoma, nonseminomatous germ cell tumor, or neural lesion. The easiest diagnoses are those of thyroid, seminoma (which has a classic picture on FNA), and parathyroid cyst (parathyroid hormone in fluid).

Lymphoma can often be definitively diagnosed and usually subtyped with FNA. The specimen can be marked to show monoclonal T or B cells, and γ and κ light chains. Diagnosis of Hodgkin’s disease poses a problem because Reed-Sternberg cells may be sparse in the specimen; however, markers exist for Reed-Sternberg cells and their variants. An inexperienced cytopathologist might have a hard time giving a confident diagnosis, but the literature supports using cytologic criteria to diagnose Hodgkin’s disease.

Thymoma presents the greatest challenge for FNA in the chest. It can, however, be differentiated from lymphoma and in some cases diagnosed securely.

Germ cell tumors show anaplastic characteristics and are not likely to be confused with other tumors, but special staining may be required to identify a specific cell type in nonseminomatous germ cell tumors.

The neurogenic tumors cause problems because of sparse cellularity and because of similarity in appearance between schwannoma and neurofibroma and between ganglioneuroma and ganglioneuroblastoma.

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**History**

Correct diagnosis of a mediastinal mass requires history taking, physical examination, appropriate imaging, relevant laboratory tests, and tissue analysis. Patients with mediastinal masses frequently have no complaints; two thirds of adults are asymptomatic. The mass often shows up on routine chest x-rays or those taken for unrelated conditions. Careful interrogation of the patient regarding systemic symptoms may help establish the diagnosis. Fears, sweats, and weight loss may indicate lymphoma or infection; night sweats and cough may suggest tuberculosis or other infectious processes; review of systems and social history may uncover a previously undiscovered HIV infection, which alters the differential diagnosis. Local symptoms like superior vena cava syndrome, hoarseness, Horner’s syndrome, or dysphagia can help localize the pathology. Symptoms may misrepresent as solid tissue.

At times MRI can add information, but in most cases it does not surpass CT. Its usefulness lies in its ability to identify flowing blood and thus determine presence of vascular lesions, including aneurysm, and to check for spinal involvement in posterior masses; MRI has completely replaced myelography to evaluate potential spinal involvement of posterior neurogenic tumors.

In suspected cases of substernal thyroid, a thyroid scan can show the precise location and extent of a patient’s functioning thyroid tissue. Most intrathoracic goiters can be diagnosed with this method. Because thyroid imaging will not work for 4 to 6 weeks following the administration of iodine-containing contrast agents, a nuclear medicine scan should precede CT when the thyroid is the suspected source of a mediastinal mass.

The gallium scan or the indium-labeled white blood cell scan may be useful in detecting mediastinal infectious processes. A dual-isotope parathyroid scan can help confirm an ectopic parathyroid neoplasm, whereas an MIBG (metaiodobenzylguanidine, a precursor of epinephrine) scan detects pheochromocytomas and neuroblastomas. Technetium-99 pertechnate scans can help identify gastric mucosa in suspected neurenerteric cysts.

Other imaging tests may help occasionally. Barium swallow can delineate the relationship of a mass to the esophagus. For anterior or posterior mediastinal masses, transcutaneous ultrasound may have some utility. Transesophageal ultrasound can delineate some visceral compartment cysts. Occasionally, angiography may supplement MRI in the definition or evaluation of a vascular lesion.

**Biochemical Markers**

Serum markers relevant to the mediastinum include AFP, β-HCG, placental alkaline phosphatase, catecholamines and their degradation products, and parathyroid hormone. The various germ cell tumors can be distinguished by a combination of these markers. Approximately 10% of mediastinal seminomas are accompanied by elevated levels of β-HCG, but not greater than 100 ng/ml; higher levels suggest nonseminomatous elements. The serum AFP level is always normal in pure mediastinal seminoma; if this measure is elevated, the mass must have nonseminomatous elements. Patients with AFP or β-HCG levels >500 ng/ml most likely have malignant nonseminomatous germ cell tumor and may be treated with chemotherapy without a biopsy. Eighty-five to 95% of these patients have at least 1 metastatic disease site, and constitutional symptoms are common, more so in pure seminoma. Elevated β-HCG or AFP levels are found in 90% of these patients, and lactate dehydrogenase value is elevated in 80 to 90%.

Test for parathyroid hormone if a parathyroid tumor is suspected, catecholamine levels if pheochromocytoma is suspected, and ferritin when neuroblastoma or ganglieneuroblastoma is considered. If there is no diagnosis after serum markers and needle biopsy, then an excisional or incisional biopsy should be performed. Excise thymomas, symptomatic thyroid masses, cysts that cannot be aspirated, and paravertebral masses. If a lymphoma or other malignant lesion is suspected, choose an incisional biopsy.

The surgical approach can range from cervical mediasti-
noscopy to full thoracotomy or sternotomy, with thoracoscopy playing an increasing role. Most of these operations require general anesthesia, which can pose a substantial risk to the patient because of airway difficulties caused by the mass pressing on the trachea and bronchi.

Radiotherapy or steroid administration may be chosen for patients in whom a safe or accurate diagnosis cannot be made. Even without a diagnosis, treatment according to the clinical presentation often results in long-term survival. Such results allow avoidance of anesthesia and biopsy when fatal complications may result.

**STAGING**

**Thymoma**

Staging takes place at operation, although a prior determination of histology helps predict prognosis and the need for adjuvant therapy. The CT aids in assessing intrathoracic spread, and CT of the upper abdomen is also indicated, as thymoma may extend below the diaphragm in up to 30% of patients. These patients require no other metastatic workup.

**Lymphoma**

Hodgkin's disease spreads by contiguity. Mediastinal Hodgkin's disease should be staged in the same way as other sites. Workup includes CT of chest and abdomen, possibly lymphangiogram and gallium scan, bone marrow biopsy, and staging laparotomy or laparoscopy if findings will alter treatment. Non-Hodgkin's lymphomas have no predictable pattern of spread; staging laparotomy thus serves no useful purpose. Workup includes CT of chest and abdomen, bone marrow biopsy, and sometimes lumbar puncture.

**Malignant Germ Cell Tumors**

Malignant germ cell tumors require CT of the chest and abdomen and other radiographic studies as suggested by symptoms.

**Poorly Differentiated Carcinoma of the Mediastinum**

Poorly differentiated carcinoma of the mediastinum, an occasional diagnosis, must be evaluated using standard guidelines for carcinoma of unknown site, ie, CT, serum markers, and bronchoscopy in older smokers. Extensive radiologic evaluation of asymptomatic sites is not required.

**Mediastinal Paragangliomas and Pheochromocytomas**

These may have higher rates of metastases than adrenal primaries. Because they have a propensity to spread to bone, a bone scan may be indicated.

**Conclusions**

Proceeding through the workup of mediastinal masses, the physician can logically proceed from step to step, based on the sex and age of the patient and the location of the mass. After chest x-ray and CT, order other imaging tests as indicated by the most likely diagnosis. Aspirate clearly cystic lesions for diagnosis and cure. Use serum tumor markers, which can definitively diagnose nonseminomatous germ cell tumors. The FNA will increasingly give a good diagnosis if the clinician, radiologist, and pathologist work closely together. Many lesions such as thymoma, enterogenous cysts, and neurogenic tumors need not have a diagnosis prior to excision. For paravertebral masses, get an MRI to check for spinal involvement. For excisional or incisinal biopsy, think of thoracoscopy. Beware of general anesthesia in patients with large anterior mediastinal masses compressing the airways. Limit the preoperative staging workup to that relevant to the specific disorder or dictated by symptoms.

These simple rules will allow the physician to proceed efficiently and logically through the workup of mediastinal masses.

**REFERENCES**