VM104  TUMORS OF THE PLEURA AND MEDIASTINUM

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THYROMAS

Thymomas are primary malignant thymic epithelial neoplasms that may show a broad spectrum of differentiation and histopathologic features (1-3). Much controversy has existed in the literature regarding the classification of thymoma. The most recent proposal by the WHO Committee for the International Histological Classification of Tumors is a formula that assigns a combination of letters and numbers to the various histologic types of thymoma from the current existing classifications (Table I). According to the authors, this proposal was not meant to represent a new histologic classification, nor was it intended to replace any previous terminology, but was rather devised as a means for facilitating comparison among the currently existing classifications (4).

Table I: Comparison of Current Histological Classifications of Thymoma

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<tr>
<td>Spindle cell thymoma</td>
<td>Medullary thymoma</td>
<td>Thymoma, well-differentiated</td>
<td>Type A</td>
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<td>--------</td>
<td>Mixed thymoma</td>
<td>“” “”</td>
<td>Type AB</td>
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<td>Lymphocyte-rich</td>
<td>Predominantly cortical</td>
<td>“” “”</td>
<td>Type B1</td>
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<td>Mixed lymphoepithelial</td>
<td>Cortical</td>
<td>“” “”</td>
<td>Type B2</td>
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<tr>
<td>Epithelial-rich</td>
<td>Well-differentiated thymic carcinoma</td>
<td>Atypical thymoma</td>
<td>Type B3</td>
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<td>Other thymic carcinoma</td>
<td>Thymic carcinoma</td>
<td>Type C</td>
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We recently introduced a simplified classification scheme for primary thymic epithelial neoplasms based on different stages of differentiation according to the presence or absence of organotypical features of the normal thymus (1). Our proposal is essentially a three-tiered classification that is patterned after standard classifications for epithelial tumors in other systems. This classification follows the rationale that thymomas, as with other malignant epithelial neoplasms, can be reliably divided according to their degrees of differentiation into 3 types: well-differentiated, moderately differentiated, and poorly-differentiated. The well-differentiated tumors are those that retain all of the organotypical features of the parent tissue and are designated by convention as thymoma. The poorly-differentiated tumors are those in which the organotypical features of differentiation are absent and the tumor cells already display conventional cytologic features associated with malignancy; such tumors have been labeled as thymic carcinomas in the literature. The third group of lesions corresponds to tumors located in-between the latter two groups and that are characterized by partial preservation of the organotypical features of the thymus but which already display cytological features of atypia; we have designated these lesions as “atypical thymoma”. The present tumor, because of its preservation of organotypical features of thymic differentiation and absence of cytologic features of malignant would correspond to a well-differentiated thymoma in our classification, or to a thymoma type B-1 in the WHO schema and lymphocyte-rich thymoma in the traditional classification.
The prognosis of thymoma remains a subject of debate. Despite the numerous reports in the recent literature, it is still generally accepted that morphology of thymoma is in general a poor predictor of prognosis. So far, the only parameter that has consistently correlated with clinical outcome in tumors displaying a well-differentiated histology has been staging at the time of initial diagnosis. The most widely accepted staging system for thymoma in use today is the one proposed by Masaoka et al (5), in which Stage I corresponds to grossly well-encapsulated tumors without microscopic evidence of capsular invasion; Stage IIa are tumors showing gross invasion into surrounding adipose tissue or mediastinal pleura, or IIb tumors showing microscopic invasion into the capsule; Stage III, tumors displaying gross invasion into adjacent organs such as pericardium, great vessels, or lung; and Stage IVa, tumors with pleural or pericardial implants, and IVb lymph-borne or blood-borne distant metastases. Kornstein et al have also noted that microscopic invasion through the capsule is associated with a significant propensity for recurrence, as opposed to invasion into the capsule, which appears not to carry the same clinical and prognostic connotation.

One unusual change in thymoma that may represent a pitfall for diagnosis if the presence of extensive cystic changes with hemorrhage and necrosis (6). Cystic change in the thymus is a well-known phenomenon that has been said to occur in up to 40% of thymomas as a focal event. Occasionally, the process may proceed to the extent that most, or all of the lesion becomes cystic (7). In the majority of such instances, the cystic changes result from extreme dilatation and coalescence of perivascular spaces. In contrast with other types of thymic cysts, the walls of the cavities in such cases are generally devoid of an epithelial lining, and inflammatory changes or lymphoid hyperplasia are not seen as part of the process.

More rarely, thymomas may be associated with secondary cystic changes of an inflammatory nature that will result in the creation of a multilocular thymic cyst (8,9). The cysts in such instances are characterized by a lining made up of squamous, cuboidal, and less frequently, ciliated columnar epithelium which is seen to merge with residual normal or atrophic thymic epithelial elements within the walls of the cyst or in continuity with dilated Hassall's corpuscles. It may be impossible to determine whether the cystic changes supervened in a preexisting thymoma or whether the thymoma developed secondarily and represents an incidental finding in cases in which the inflammatory/cystic changes predominate and the thymoma is found incidentally as a small mural nodule attached to the wall of a cyst.

**Differential diagnosis:**

On occasion, thymomas with a lymphocyte-rich histology may be extremely difficult to differentiate from a malignant lymphoma on frozen section examination and one may have to defer to permanents. Inking and extensive sampling of the capsule on the gross specimen is of prime importance in the microscopic assessment of thymomas, and the pathologist should never rely on the surgeon's operative impression regarding invasiveness for the staging of these tumors.

Much has been made about the cytokeratin patterns of expression in thymoma, and the lymphoid cell immunophenotype for the diagnosis of thymoma (10,11). The fact is that the diagnosis of thymoma remains an H&E diagnosis. Immunohistochemical stains, electron microscopy, and other special techniques remain of limited value in these tumors. Moreover, more important than specific subtyping of well-differentiated variants of thymoma is making the correct diagnosis and not mistaking this tumor for other types of lesions that may present
in a similar anterior mediastinal location. The most important prognostic factor for the clinical evaluation and prognostication of these tumors remains the status of capsular integrity. Tumors that are completely encapsulated at the time of initial diagnosis are practically cured by complete surgical excision; whereas invasive or incompletely excised lesions tend to recur and can occasionally metastasize. Adequate inking of the outer surface of the specimen and extensive sampling of the capsule are therefore of primary importance for the evaluation of these tumors.

Reference:

THYMIC CARCINOMA

Thymic carcinomas are defined as primary thymic epithelial neoplasms displaying overt cytologic features of malignancy which have already lost all of the organotypical features characteristic of the thymus (1-7). These tumors had until recently been a highly controversial entity, primarily due to the lack of agreement regarding their definition and the proper criteria for diagnosis. Another problem for the study of these tumors stemmed from the fact that they can show extreme morphologic diversity, with a wide variety of histologic growth patterns and types having been described (1,2).

The largest series of thymic carcinoma published in 1991 studied 60 patients who had been followed for at least 3 years or until their time of death (2). Two clinically distinct groups of patients were identified: 1) one that followed a relatively favorable clinical course with long survival, and 2) one that followed a rapidly fatal outcome. The tumors in the first group were composed of carcinomas of low-grade histology characterized by good gross circumscription, partial preservation of lobular growth pattern on histologic examination, absence or minimal nuclear atypia and necrosis, and low mitotic activity, whereas those in the second group showed the opposite features, namely extensive infiltration of adjacent structures, marked nuclear atypia, frequent areas of necrosis, increased mitotic activity and high-grade histology.

On the basis of the above observations, thymic carcinomas were classified into low-grade and high-grade histology groups. The tumors in the low-grade histology group included well-differentiated squamous carcinoma, mucoepidermoid carcinoma, and basaloid carcinoma. The tumors in the high-grade histology group included poorly-differentiated squamous cell (lymphoepithelioma-like) carcinoma, small cell/ neuroendocrine carcinoma, clear cell carcinoma, sarcomatoid carcinoma, and anaplastic/undifferentiated carcinoma (2).

<table>
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<tr>
<th>Thymic Carcinoma - Histologic Variants</th>
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<tr>
<td><strong>Low-Grade Histology:</strong></td>
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<tr>
<td>- Well-differentiated squamous cell</td>
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<tr>
<td>carcinoma</td>
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<tr>
<td>- Well-differentiated mucoepidermoid</td>
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<tr>
<td>carcinoma</td>
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<td>- Basaloid carcinoma</td>
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<tr>
<td><strong>High-Grade Histology:</strong></td>
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<tr>
<td>- Poorly-differentiated (lymphoepithelioma-like)</td>
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<tr>
<td>- non-keratinizing squamous carcinoma</td>
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<td>- Poorly-differentiated mucoepidermoid carcinoma</td>
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<td>- Small cell/ neuroendocrine carcinoma</td>
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<td>- Sarcomatoid carcinoma</td>
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<td>- Anaplastic/undifferentiated carcinoma</td>
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The relationship of thymic carcinoma with thymoma has been for many years poorly understood. In a recent study, we identified 22 patients in whom a thymic carcinoma was seen to develop in close association with a morphologically conventional thymoma (8). Several instances of this phenomenon have also been previously reported in the literature (9-11). Shimosato et al, in their series of squamous cell carcinoma of the thymus described one case in which transitions were found between the squamous elements and areas of benign thymoma (9). Wick et al later documented a case of sarcomatoid thymic carcinoma complicating an epithelial-rich thymoma. More recently, Kuo et al described two cases among 13 thymic carcinomas in which a lymphoepithelioma-like carcinoma and a squamous carcinoma were seen to arise from a preexisting thymoma (5). The present case represents...
another example of this phenomenon, whereby a high-grade malignancy supervenes on a long-standing thymoma.

The most common form of thymic carcinoma in our experience is the poorly-differentiated, non-keratinizing (lymphoepithelioma-like) carcinoma of the thymus. Although it was initially thought that these tumors, like their counterparts in the nasopharynx, were invariably associated with EBV infection, a recent study has shown that not all cases of lymphoepithelioma-like carcinoma of the thymus will test positive for EBV genomic sequences (12).

Our experience suggests the existence of a continuous spectrum of differentiation between thymoma and thymic carcinoma. Such evidence would support the notion that the process of tumorigenesis in thymoma and thymic carcinoma obeys a multistep process, such as has been demonstrated for many other types of malignancy. Demonstration of a multistep process of carcinogenesis in this setting would support the notion that the different morphologic types of thymic epithelial neoplasms are histogenetically very closely related. This information is of more than academic interest, since it would force us to acknowledge the fact that some of the sharp divisions and criteria we have devised for the classification of these tumors may be more arbitrary than real.

References:

GERM CELL TUMORS OF THE MEDIASTINUM

Primary mediastinal germ cell tumors (GCT) account for approximately 20% of all anterior mediastinal tumors and cysts, and essentially recapitulate those seen in the gonads. The etiology of these tumors occurring in the mediastinum is still unknown; however, some authors consider that their occurrence is due to misplaced germ cells during migration, which get embedded along midline structures. Clinically, the same as their counterparts in the gonads, mediastinal GCT can be associated with conditions such as Klinefelter’s syndrome and lymphoproliferative disorders. Histologically, mediastinal GCT are similar to those in the gonads. However, the distribution of these tumors does not correlate with those seen in the gonads. Even though these tumors have been reported in female patients, in our experience, we have seen only a few cases (teratomas) in female patients. Non-teratomatous tumors have been encountered exclusively in men (1-12).

In our experience, teratomatous lesions are by far the most common in the mediastinal area. Among these tumors, teratomas composed of mature elements are the most frequently encountered. Teratomas with malignant component (carcinoma or sarcoma) represent a sizable number of cases while pure immature teratomas are far less common. Needless to say, combinations of teratomatous lesions containing mature, immature, and malignant components are common.

Among the non-teratomatous tumors, seminoma is the most common in the anterior mediastinum. The tumor usually presents as a large, non-encapsulated mass in young adult males. Histologically, mediastinal seminomas are similar to those occurring in the gonads. However, mediastinal seminomas may show other features such as cystic changes similar to those seen in multilocular thymic cyst, extensive granulomatous reaction, lymphoid follicular hyperplasia, and hyperplastic remnant of thymic tissue. Because of these unusual features the differential diagnosis of mediastinal seminoma may include benign lesions such as multilocular thymic cyst or malignant lesions such as Hodgkin’s lymphoma and large cell lymphoma.

Contrary to teratomatous and seminomatous tumors of the mediastinum, non-seminomatous tumors are far less frequent. Usually, when they occur, non-seminomatous tumors present as bulky anterior mediastinal masses with hemorrhage and necrosis. Like those in the gonads, non-seminomatous tumors in the mediastinum are represented by yolk sac tumor (endodermal sinus tumor), embryonal carcinoma, and choriocarcinoma. Of course, these tumors may appear in their pure form or in combination. One of the most common combinations of these tumors is that of embryonal carcinoma and yolk sac tumor. In this setting, clinical information such as serum levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and carcinoembryonic antigen, are useful markers not only to follow-up these patients for possible recurrences but also to properly sample the tumor in case only one of those components are represented in the material examined. Histologically, yolk sac tumor is by far the more versatile with several histopathological growth patterns. The most common growth pattern is that of sheets of tumor cells arranged in a microcystic pattern composed of rather small round cells with little pleomorphism and mitotic activity, and with the presence of Schiller-Duval bodies. Other histological growth patterns that may pose more difficulty in their diagnosis include the intestinal, hepatoid, and spindle cell variant.

In cases of embryonal carcinoma, because of the histology of the neoplasm, the tumor may mimic a poorly differentiated adenocarcinoma. Embryonal carcinoma is
composed of anastomosing ducts or glands with large primitive cells admixed with areas of hemorrhage and necrosis. However, the clinical information of an anterior mediastinal mass in a relatively young patient should lead to the correct interpretation. The same applies to cases of mediastinal choriocarcinoma. In most cases, at the time of the diagnosis, the tumor has spread within the thoracic cavity (lungs) and/or outside of it. Because there are primary pulmonary carcinomas with prominent syncytiotrophoblast-like component, pure mediastinal choriocarcinomas may pose a problem in interpretation. The finding of a predominantly anterior mediastinal tumor with cytotrophoblastic component should lead to the correct interpretation.

The use of immunohistochemical studies in the diagnosis of mediastinal GCT plays an important role in ruling out other conditions that may be confuse with GCT. In cases of seminoma, the use of keratin and PLAP is helpful while in non-seminomatous tumors keratin, AFP, and HCG may prove beneficial as an aid in their diagnosis. One important factor to keep in mind is the positive staining that may be seen with CD-30 in cases of embryonal carcinoma. In this setting, it would important to performed additional studies since anaplastic large cell lymphomas are also known to have positive staining for EMA, CD45 and CD3. The use of CEA, keratin, AFP, and ALK-1 may help in difficult cases. On the other hand, in cases of teratomatous lesions in which there are sarcomatous elements, the use of other markers may be helpful.

References:


SPINDLE CELL TUMORS OF THE MEDIASTINUM

Spindle cell tumors of the mediastinum are extremely rare. In the anterior mediastinal compartment, the vast majority of such lesions represent spindle cell thymomas. Other types of spindle cell tumors of the mediastinum include metastases from sarcomatoid (spindle cell) carcinoma of the lung, metastasis of spindle cell melanoma, and a variety of spindle cell sarcomas. In the posterior mediastinum, the most common types of spindle cell tumors are represented by neurogenic tumors, including schwannomas, neurofibromas, and malignant peripheral nerve sheath tumors. In our experience in reviewing a large number of spindle cell tumors of the mediastinum, the most common type that we have encountered in this location has been solitary fibrous tumor.

Solitary fibrous tumor is a lesion that is most commonly seen arising from serosal surfaces such as the pleura. The tumor has been known by different designations including fibrous mesothelioma, submesothelial fibroma, and localized fibrous tumor. Similar lesions have been described in many other locations including orbit, thyroid liver, and mediastinum. Witkin and Rosai (1) were the first to recognize this lesion as the mediastinal counterpart of the one occurring in the pleura. Although this tumor was regarded for many years to originate from mesothelial cells, more recent studies have shown that the tumor cells have features of submesothelial fibroblasts (2-11). More recently, strong and consistent immunoreactivity has been demonstrated in the tumor cells of this lesion for CD34, a hematopoietic progenitor cell marker that provides an added discrimination parameter for the identification of these tumors (11). In addition, other markers such as Bcl-2, another marker commonly used in hematopathologic malignancy, has been shown to have a positive reaction in these tumors.

The diagnosis of SFT in atypical locations can be fraught with difficulties because of their variegated histopathologic appearances. The tumor has the capability of adopting a variety of growth patterns that can closely mimic a number of soft tissue neoplasms (12). Thus, the fascicular, storiform, herringbone, and palisading growth patterns seen in these tumors may simulate fibrosarcoma, synovial sarcoma, neurogenic sarcoma, and hemangiopericytoma.

The two conditions with which these tumors are most often confused are hemangiopericytoma and benign or malignant peripheral nerve sheath tumors (12). Hemangiopericytoma has become more and more a diagnosis of exclusion, as new immunohistochemical markers have allowed us to realize that a great variety of soft tissue neoplasms may adopt this growth pattern, including synovial sarcoma, leiomyosarcoma, mesenchymal chondrosarcoma, and solitary fibrous tumor. Other features of importance for diagnosis when located on serosal surfaces is the characteristic polypoid, pedunculated gross appearance, and the admixture of hemangiopericytic areas with other patterns of growth not commonly seen in hemangiopericytoma on histology.

Distinction from peripheral nerve sheath tumors (benign and malignant schwannomas) may be quite difficult both by light microscopy and with immunohistochemistry, since the neural marker, S-100 protein, may not be expressed in a high percentage of cases. Electron microscopy may be the only means of settling the issue under such circumstances by demonstrating the distinctive ultrastructural features of schwannian neoplasms.
SFT in mediastinal locations will introduce added difficulties for diagnosis. An important consideration for differential diagnosis at this site is spindle cell thymoma or sarcomatoid thymic carcinoma. Immunohistochemical stains will play a major role in this setting by allowing identification of the epithelial nature of the spindle cells with the use of keratin antibodies. Another potential pitfall in diagnosis is mistaking these tumors for other types of unusual sarcomas in the mediastinum, such as MFH, rhabdomyosarcoma, and synovial sarcoma. The frequent and prominent stromal pattern often observed in these tumors, coupled with the presence of fibrohistiocytic-type giant cells occasionally seen in SFT may raise the question of MFH in the differential diagnosis. In the truly malignant cases, making this distinction may constitute a moot point; however, we have observed cases in which a pleural tumor originally diagnosed as MFH because of marked cellular pleomorphism, high mitotic activity, and areas of necrosis, behaved in an entirely benign fashion. In those cases, despite histologic atypia and features of malignancy, the tumors were grossly well-circumscribed, polyoid and encapsulated. Gross morphology thus appears to be of major significance for prognosis in these tumors.

We have also observed examples of spindle cell sarcomas with features of monophasic synovial sarcoma arising as primaries in the mediastinum. Focal immunoreactivity for keratin and EMA in such cases will readily distinguish them from SFT. Leiomyosarcomas may also present as a primary lesion originating from the soft tissues in either the anterior or posterior mediastinal compartment (13). The prominent fascicular appearance of the cells which intersect at right angles, the presence of muscle markers by immunohistochemistry, and ultrastructural features of smooth muscle differentiation will establish the diagnosis for these tumors in most cases. Finally, embryonal rhabdomyosarcoma with a spindle cell growth pattern can also occur in the mediastinum (14); demonstration of the myogenic nature of the tumor can generally be accomplished with actin, desmin, and myoglobin antibodies.

The behavior of these tumors may be difficult to predict on the basis of histologic features. Increased number of mitoses and areas of necrosis have been felt to correlate with aggressive behavior by some (4). Gross morphologic features such as encapsulation and polyoid configuration may be difficult to assess under certain circumstances, such as in mediastinal, intrapulmonary, and other extrapleural locations. Complete surgical excision will be curative in the vast majority of lesions.

References:

Primary malignant tumors of the pleura are in general dominated by malignant mesothelioma. Not only is it the most common malignant tumor of the pleura but also the one that poses most difficulties in the diagnosis. Due to its legal implications and its varied histopathological appearance, mesotheliomas have been the subject of extensive studies. Interestingly, malignant mesotheliomas are unusual tumors and it has been estimated that their incidence in the United States is approximately 3 to 7 cases per one million persons in the population per year. Although mesotheliomas have been associated with exposure to asbestos fibers, approximately 50% of individuals affected by mesotheliomas do not have a history of asbestos exposure, leading to believe that their etiopathology may be multifactorial and not limited to the exposure of asbestos fibers. However, those cases in which there is an association with exposure to asbestos are the ones that generally gain more attention because they are the ones that are usually followed by legal counsel.

In general mesotheliomas are more common in adults over 50 years of age. In those cases in which the tumor is associated with asbestos, the patient had usually been exposed for over 15 years to the asbestos fibers. The stated latency period for asbestos in mesothelioma varies from 15 to 60 years, thus, it would be very unusual to find a case in which the tumor is linked to asbestos in a patient with only a few years of exposure. One other debated issue is the type of asbestos fibers that produce mesotheliomas; arguments for some fibers being non-carcinogenic have been made. This latter issue is one usually brought up in court by the legal system attempting to defend a particular exposure to asbestos fibers. In this review, we will not explore that issue and will reserve it for the legal establishment. Nevertheless, a documented history of asbestos exposure of more than 15 years is a powerful argument in favor of linking asbestos and mesothelioma in a particular case. What is more interesting is the fact that mesotheliomas, as stated before, can occur in the setting of a negative history of asbestos exposure. Examples of it are the cases that have been described in children and housewives. Other possible etiopathologic causes for the development of mesothelioma include radiation, chronic inflammation, viral infections, and diethylstilbestrol.

Clinical Features:
Clinical and radiological information play a highly important role in the diagnosis of mesothelioma. Ignoring clinical and radiological information may conduce to an erroneous diagnosis even by the most experienced pathologist. History of longstanding exposure to asbestos whether factual or not, should lead to a careful analysis of a particular biopsy material from any individual. However, one of the most important aspects in the diagnosis of mesothelioma is the radiological evaluation. Either a plain chest radiograph or more sophisticated studies such as computerized tomography represent important tools in the evaluation of a possible case of mesothelioma. In cases in which a question of mesothelioma arises, one should inquire into the following aspects:
- Is there diffuse involvement of the pleura (studding by nodules)?
- Are there intraparenchymal tumor nodules or masses (peripheral)?
- Is there diffuse thickening of the pleura?
- Is there encasement of the lung?
- Is there unilateral or bilateral pleural involvement?
- Is there a localized pleural-based tumor mass?
A careful analysis of the radiological studies with the appropriate material for histopathological evaluation should lead both the clinician and the pathologist to seek the necessary tools in order to arrive at a more specific diagnosis. In this regard, many times the clinical and radiological aspects of the cases are clear but the available material for histopathological examination is not adequate. In such circumstances, one should not make a definitive diagnosis but rather raise the level of suspicion and request additional material if clinically indicated. Part of this rationale is the fact that the surgical treatment for cases of mesothelioma can be extreme, thus, it is imperative for a pathologist to be absolutely sure about the diagnosis. Furthermore, it is well known that there are other pleural conditions of an inflammatory nature that may clinically and radiologically mimic malignant mesothelioma. Therefore, one should use the clinical and radiological information not to make a diagnosis per se but rather to orient oneself in the plan to follow with the use of immunohistochemistry and/or electron microscopy. Ultimately the diagnosis of mesothelioma is a pathological one and not a clinical or radiological diagnosis alone.

**Pathological Features:**

**Gross features:**
Mesotheliomas are tumors with a characteristic gross appearance that rarely pose a problem for the diagnosis. The tumor will show diffuse pleural involvement. In some cases, the tumor follows the intrapulmonary septum and in rare instances the tumor may involve the lung parenchyma with small nodules in the surface of the lung parenchyma. However, the presence of a well-defined tumor mass in the periphery of the lung, even if the tumor also shows diffuse pleural involvement, should alert the pathologist to the possibility of an adenocarcinoma with diffuse pleural involvement. Such tumors have been designated as pseudomesotheliomatous adenocarcinoma due to its similar gross appearance to malignant mesothelioma.

**Histopathologic characteristics:**
Mesotheliomas may show a variety of histopathological growth patterns. However, traditionally mesotheliomas have been divided into three categories:
- Epithelioid
- Sarcomatoid
- Biphasic (combination of epithelial and sarcomatoid)

**Epithelioid Mesothelioma:**
Probably the most common of the three variants, it has been estimated that it represents about 70% of all mesotheliomas. Several distinct histopathological growth patterns of epithelioid malignant mesothelioma have been described and in some occasions may represent a diagnostic challenge. Among the variants that have been recognized are:
- Tubulopapillary
- Epithelioid
- Deciduoid
- Clear cell
- Glandular
- Myxoid
- Adenomatoid

It is comforting to know that among these growth patterns, the epithelioid and tubulopapillary are the most common. Nevertheless, it is very important to be at least
theoretically familiar with the other more unusual growth patterns in order to properly direct our differential diagnosis. Regardless of the histopathological growth pattern, whether the tumor shows clear cell change, myxoid areas, glandular differentiation, or an adenomatoid pattern, one can not overlook the fact that radiologically the tumor is involving diffusely the pleura. This latter fact should alert and lead the pathologist to at least rule out the possibility of mesothelioma. Thus, the use of histochemical and immunohistochemical studies becomes a crucial factor in the evaluation of such lesions.

Histochemical studies:

Traditionally and before the advent of immunohistochemistry, histochemical studies played an important role in the diagnosis of mesothelioma. Currently in some circumstances they can solve the problem easily in the more banal cases. The use of periodic acid-Schiff with and without diastase digestion, mucicarmine, and Alcian blue has been used in the past with relative success. It is important to state that although the positive finding of intracellular mucin is a strong feature of adenocarcinoma, this finding has also been reported in up to 5% of the cases of mesothelioma. On the other hand, it is also important to note that some mesotheliomas will show abundant extracellular mucin; in the majority of instances, the extracellular mucin will be composed of hyaluronic acid and will be strongly positive for Alcian blue and the reaction will be abolished following treatment with hyaluronidase. With the advent of immunohistochemistry there has been a tendency to bypass the use of histochemical stains for the evaluation of mesothelioma.

Immunohistochemical studies:

A great deal of information regarding immunohistochemical studies in the evaluation of mesotheliomas is available. Numerous studies attempting to positively identify mesotheliomas have been published, some of them with relative success. However, the immunohistochemical diagnosis of mesothelioma has in general been considered one of exclusion. Although there are essentially dozens of immunohistochemical markers that have been investigated for the diagnosis of mesothelioma, the fact is that only a few are of practical use.

Currently, the most commonly employed markers for the diagnosis of mesothelioma vs. adenocarcinoma in the pleura include broad-spectrum keratin, keratin 5/6, calretinin, CEA, MOC31, Leu-M1, B72.3, and Ber-EP4. Some of these markers have been stated to specifically stain mesothelial cells (e.g., keratin 5/6 and calretinin) while other have been stated to identify only cases of adenocarcinoma (CEA, MOC-31 and Leu-M1). Broad-spectrum keratin obviously stains both tumors while Ber-EP4 has been found to be positive in up to 27% of cases of mesothelioma. It is exactly in the setting of an epithelioid mesothelioma where all these markers become important in the evaluation of the tumor. However, one should mention that even though these immunohistochemical markers are very important, positive staining does not constitute a full-proof diagnosis of the tumor. In some instances, the choice of antibody may influence the result. An example of this is CEA, which has been demonstrated to show focal positivity for malignant mesothelioma in about 5% of cases. This may be explained by the use of antibodies produced with unabsorbed heteroantiserum to CEA. The use of monoclonal CEA appears to be more reliable for making this evaluation.

In short, we can summarize the immunohistochemical studies the following way: if the tumor in question shows positivity for broad-spectrum keratin, keratin 5/6, or calretinin, this supports the diagnosis of malignant mesothelioma. However, if there is positive staining for
one or more antibodies to CEA, MOC31, Leu-M1, B72.3 or other carcinomatous epitope, then the diagnosis of adenocarcinoma is favored.

**Electron Microscopic studies:**

The use of ultrastructural studies in cases of mesothelioma is very important due to the specific features of malignant mesotheliomas. However, the use of ultrastructural studies in many cases is hampered by the lack of material when it is needed the most. Most of the time, the material does not become available until there is a more extensive procedure while in the majority of the cases the initial biopsy (which is the one in which one needs to establish the primary diagnosis prior to surgery) is the only material available.

The use of electron microscopy is mainly helpful in the better-differentiated cases while those in which the tumor is poorly differentiated the ultrastructural findings will rarely be helpful. Such tumors are characterized by the presence of slender, undulating microvilli that are much longer than those normally encountered in conventional adenocarcinomas. Additionally, the cells with display frequent well-developed intercellular junctions, and there will be absence of intracytoplasmic secretory vacuoles or intracellular lumina as is commonly seen in adenocarcinomas. Usually in most cases in which immunohistochemistry has failed to provide a clear interpretation of a lesion, results of electron microscopy will also be questionable. Nevertheless, it can be very helpful in many instances and one should make every effort to obtain a sample for such studies, even when your institution does not have a functioning electron microscope because the tissue can always be sent out to a specialized facility.

**Differential Diagnosis:**

In the setting of an atypical epithelial cellular proliferation of the pleura the most important conditions to rule out are either an adenocarcinoma that has extended into the pleura, a metastatic epithelial tumor of other origin, or a mesothelial hyperplasia. If one has concluded that the cellular proliferation in question is malignant, then the use of immunohistochemical studies as previously mentioned will be the next step. The interpretation can be more difficult in cases of mesothelial hyperplasia. In this setting, there is no immunohistochemical stain which can separate a neoplastic cellular proliferation from a hyperplastic one. Thus, even though one has followed the necessary steps, it is imperative not only to correlate the histology with the clinical and radiological features but also to properly interpret the results of the immunohistochemical studies. As a matter of fact even electron microscopic studies would fail to separate such cellular proliferations. In essence the diagnosis of mesothelial hyperplasia is a morphologic one and one that requires careful attention to specific features (see tables 1 and 2).
Table 1:  

**Histopathological features of Mesothelioma vs Mesothelial Hyperplasia**

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<thead>
<tr>
<th>Feature</th>
<th>Mesothelioma</th>
<th>Hyperplasia</th>
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<tbody>
<tr>
<td>Penetration into adipose tissue or muscle</td>
<td>+++</td>
<td>---</td>
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<tr>
<td>Stromal invasion</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Inflammation</td>
<td>--</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular atypia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mitoses</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cellular proliferation in surface</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Granulation tissue</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Fibrin</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

Table 2:  

**Immunohistochemical Features of Mesothelioma and Adenocarcinoma**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Adenocarcinoma</th>
<th>Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Leu-M1</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>B72.3</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Ber-ep4</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Calretinin</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Keratin 5/6</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Broad-spectrum keratin</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>EMA</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

**Sarcomatoid Mesothelioma:**

This variant of mesothelioma is less common than the epithelioid one and probably represents less than 15% of all these tumors in its pure form. As its name implies, the tumor characteristically has a growth pattern of spindle cells with elongated nuclei and inconspicuous nucleoli in a manner mimicking a sarcoma of soft tissues. Due to the presence of extensive collagenization there have been several histopathological growth patterns recognized that are very important:

- Spindle cell type (fibrosarcoma-like or MFH-like)
- Desmoplastic variant
- Lymphohistiocytoid
Of these variants, the desmoplastic variant presents a special difficulty since it can be incorrectly diagnosed as a benign fibrous pleurisy. However, when the tumor exhibits all the features of malignancy, i.e., necrosis, cellular atypia, mitotic activity with atypical mitoses, stromal and adjacent soft tissue invasion, it is of importance to rule out a sarcomatoid carcinoma with extension into the pleura or a sarcoma of soft tissue. The presence of an atypical spindle cell proliferation with stromal invasion and necrosis is usually a good sign of a sarcomatoid mesothelioma.

By far the most difficult diagnosis is that of desmoplastic mesothelioma. In such cases, the pleural biopsy may show extensive collagenization and only a paucicellular proliferation that may not show marked cytologic atypia. In such cases, morphologic characteristics such as stromal invasion, adjacent tissue invasion, i.e., adipose tissue and muscle are important features to identify the process as malignant. Nevertheless in limited (small) pleural biopsies, the diagnosis may not be apparent and one can only make the suggestion of desmoplastic mesothelioma if the clinical and radiological findings are in keeping with such diagnosis.

**Histochemical studies:**

The use of histochemical studies such as PAS with and without diastase digestion, mucicarmine stain, and alcalin blue stain with hyaluronic acid digestion has progressively lost its role in the diagnosis of these tumors. With the advent of immunohistochemical stains, more sensitive methods have been made available in the armamentarium for the diagnosis of malignant mesothelioma. In any event, positivity of the tumor cells for Alcian blue with hyaluronidase favors a diagnosis of malignant mesothelioma, whereas PAS and mucicarmine positivity are more in favor of adenocarcinoma.

**Immunohistochemical studies:**

In the setting of a spindle cell mesothelioma, whether the tumor is desmoplastic or not, the role of immunohistochemistry is relatively limited since most of the antibodies used in regular epithelial mesotheliomas have no practical use in sarcomatoid mesotheliomas. The use of broad-spectrum keratin is by far the most important of them. All other carcinomatous epitopes are known not to react with sarcomatoid tumors. In addition, the use of calretinin and keratin 5/6 is rather limited since its positivity may vary and negative results do not mean that the tumor in question is not a mesothelioma. Furthermore, because of the lack of more specificity from immunohistochemical markers, the issue of fibrous pleurisy and desmoplastic mesothelioma cannot be solved by immunohistochemistry since both lesions may cross-react with keratin antibodies.

**Differential Diagnosis:**

In cases in which there is no doubt about the neoplastic nature of the tumor, the most important differential diagnosis is with another spindle cell neoplasm of mesenchymal origin. In this case, the use of proper immunohistochemical studies and/or electron microscopy will lead to a more appropriate interpretation. In cases of sarcomatoid carcinoma of the lung involving the pleura in a diffuse manner, the finding on radiographic studies of an intrapulmonary tumor mass will lead to a correct interpretation. By far the most difficult diagnosis is with fibrous pleurisy of a reactive or inflammatory nature. In these cases, the diagnosis is based on morphologic grounds alone since immunohistochemistry cannot resolve the problem (see table 3).
Table 3:

**Histopathological Features of Sarcomatoid Mesothelioma and Fibrous Pleurisy**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mesothelioma</th>
<th>Fibrous Pleurisy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitions between cellular and acellular</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Cellular atypia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Granulation tissue</td>
<td>--</td>
<td>++</td>
</tr>
<tr>
<td>Fibrin</td>
<td>--</td>
<td>++</td>
</tr>
<tr>
<td>Inflammatory reaction</td>
<td>--</td>
<td>++</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Immunohistochemistry**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mesothelioma</th>
<th>Fibrous Pleurisy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad-spectrum keratin</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Keratin 5/6</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Calretinin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smooth muscle actin</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Biphasic Mesotheliomas:**

As its name implies these tumors are composed of a mixture of epithelial and sarcomatoid areas. As a rule one should have unequivocal sarcomatoid areas and/or epithelial areas in order to call a case biphasic. One important differential diagnosis with biphasic mesothelioma is the fact that primary synovial sarcoma of the pleura have been described that can be easily confused for these tumors. However, in that setting, the tumor is a localized pleural-based mass without diffuse involvement of the pleura. Once again, close clinical and radiological correlation is highly advised in that setting.

**Other Variants:**

In very unusual cases, mesotheliomas have been encountered that show extensive areas of cartilage and bony metaplasia. In these cases, a small biopsy may not sample representative areas, which may pose a diagnostic challenge for the pathologist. In addition, due to its rarity, one should be familiar with these unusual features to properly diagnose those cases as mesotheliomas with osseous and cartilaginous component instead of naming those tumors by another name, such as pleuropulmonary blastoma or carcinosarcoma of the pleura.

**Treatment and Prognosis:**

One of the most common modalities of treatment is extrapulmonary pneumonectomy. In some centers this procedure is performed only for epithelioid mesotheliomas while in others it is done for all mesotheliomas. It appears that the procedure increases the survival of these patients by a few months. However, in the majority of cases the prognosis is still poor with survival rates of no more than 12 to 18 months after diagnosis. In view of the widespread acceptance of this procedure, now more than ever the diagnosis of
mesothelioma is one that requires a careful attention not only to the histology of the tumor but also to the clinical and radiological aspects.

**PRACTICAL APPROACH:**

Since the diagnosis of mesothelioma is multifactorial, the following is our approach to these lesions, which can be applied in the majority of cases:

- Detailed clinical history
- Detailed radiological information
- Adequate biopsy material
- Immunohistochemical studies
- Electron microscopy

**Clinical Setting:**

- If the tumor is epithelial, then the use of a battery of immunohistochemical studies is in order and these include: keratin 5/6, calretinin, CEA, MOC31, and Leu-M1, B72.3, or Ber-EP4.
- If the tumor is sarcomatoid, then the immunohistochemical studies can be limited to broad-spectrum keratin. Keratin 5/6 and calretinin can be added to this panel, however, it is well known that those antibodies may be negative in sarcomatoid mesotheliomas. Other immunohistochemical markers for ruling out other mesenchymal neoplasms (such as S-100 protein/HMB45 for melanoma or SMA for leiomyosarcoma) may be included depending on the degree of suspicion.

**References:**


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EPITHELIOID CELL SARCOMAS OF THE MEDIASTINUM

Sarcomas composed of epithelioid cells are very rare in the mediastinum. Their main importance lies in appropriately distinguishing them from other epithelioid cell tumors with which they can be confused, such as thymoma, thymic carcinoma and a variety of metastatic malignant neoplasms to this region. Epithelioid sarcoma as described in the superficial soft tissues has not been described as arising as a primary lesion in the mediastinum, but we have encountered occasional metastases to mediastinal lymph nodes from well-documented examples of these tumors. Malignant peripheral nerve sheath tumors arising either in the posterior or, more rarely, the anterior mediastinum, can occasionally adopt an epithelioid appearance, but the latter circumstance is distinctively rare. The most common type of epithelioid mesenchymal tumor in the mediastinum in our experience has been epithelioid hemangioendothelioma.

Epithelioid hemangioendothelioma is a term that was first introduced by Weiss and Enzinger (1) to describe a distinctive soft tissue neoplasm that showed intermediate features between a benign hemangioma and an angiosarcoma. Because of their striking epithelioid features, the tumors were often misdiagnosed as metastatic carcinoma. Tumors with identical features have now been recognized in several organs, including the skin, lung, liver, bone and spleen (2-4).

Epithelioid hemangioma arising as a primary tumor in the mediastinum is extremely rare. Very few reports have been presented in the literature on this condition, mostly as case reports. We had the opportunity to examine a series of 12 cases these neoplasms arising in the mediastinum (5). The age of the patients in our study ranged from 19-62 years (mean: 49.4 years); 3 were women and 9 were men. Seven patients presented with symptoms due to compression of surrounding structures; the rest were asymptomatic and discovered on routine chest X-rays. The tumors measured 4.5 to 13.5 cm in greatest diameter and were well-circumscribed and encapsulated in 7 cases and locally infiltrative in 5. Histologically, the lesions showed a spectrum of features including those classically described for low-grade epithelioid hemangioendothelioma in soft tissue, to tumors showing more pronounced cytologic atypia with mitotic activity and focal areas of necrosis. An interesting feature of these tumors was the existence of foci of metaplastic bone formation accompanied by osteoclast-type giant cells in five of our cases, as well as foci of intravascular papillary tufting seen in four (6,7). The explanation for the presence of the latter is still unclear. It has been postulated that tumor hemorrhage may be responsible for generating chemoattractant factors that will trigger the osteoclast-type reaction.

Immunohistochemical studies showed strong positivity of the tumor cells in our cases for Factor-VIII-related factor (von Willebrand’s factor), CD31 and vimentin, as well as focal positivity for Ulex europaeus lectin. Interestingly, keratin stains were negative in all cases, as well as in all other cases of mediastinal epithelioid hemangioendothelioma reported in the literature in which the stains were performed. This stands in contrast with the findings reported in the literature for this tumor at other locations, which have shown strong positivity for keratin antibodies in the tumor cells (8). Electron microscopic studies confirmed the vascular endothelial nature of the tumor cells in our cases.

Clinical follow-up of our patients showed that 7/8 patients were alive and well without evidence of disease from 2-21 years (mean: 8 years). It was concluded that, despite the ominous clinical, radiographic and histologic features, epithelioid hemangioendothelioma of the anterior mediastinum most likely represents a low-grade malignant neoplasm that may be...
adequately controlled in most instances with surgery alone (5). We have since encountered three additional cases in which the lesions recurred and metastasized to the lung after a period of 2-5 years following surgery, including one case in which the lesion was multifocal at the time of presentation and involved both the mediastinum and lung. An aggressive but conservative approach therefore appears to be warranted for the management of these tumors.

Differential diagnosis:

The differential diagnosis for this condition is essentially that of other epithelioid cell tumors of the mediastinum (see Table I). As with their primary soft tissue counterparts, the most immediate differential diagnosis is with primary or metastatic carcinoma, particularly from the lung, breast, pleura and head and neck primaries. Lung cancers metastatic to the anterior mediastinum, with the exception of small cell neuroendocrine carcinoma, usually will disclose a mass lesion in the lungs on chest X-rays and CT scans. Additionally, they will be characterized by more pronounced cytologic atypia and will more often be present within lymph nodes. Enlarged mediastinal lymph nodes can rarely be the initial manifestation of metastatic malignant mesothelioma; such lesions will be characterized by a proliferation of bland-appearing round to polygonal tumor cells with minimal cytologic atypia. The clue to the identification of the metastatic nature of the process lies in the identification of lymph nodal elements, such as lymph node sinuses and abundant plasma cells in the stroma.

Metastases from breast carcinoma to mediastinal nodes will usually require knowledge of the history and comparison of the lesion with the original tumor for confirmation. A highly distinctive feature of epithelioid hemangioendothelioma is the presence of prominent cytoplasmic vacuoles in the tumor cells representing abortive vascular lumina. Unfortunately, in some instances, this feature may lead to a prominent signet-ring cell appearance that may be confused for metastasis from signet-ring cell carcinoma from the lung and other organs. The absence of mitotic activity, necrosis or cytologic atypia should alert the pathologist to this possibility and prompt the inclusion of vascular endothelial markers in the panel of immunohistochemical stains.

Distinction of epithelioid hemangioendothelioma from primary thymic carcinoma can also represent a pitfall for diagnosis. Familiarity with the different histopathologic varieties of thymic carcinoma will be of value in this setting (9, 10). Primary thymic carcinoma is characterized by its ability to resemble other types of well-established cancers occurring in other epithelial organs, such as squamous cell carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, spindle cell carcinoma and lymphoepithelioma-like carcinoma. The diagnosis of primary thymic carcinoma is one of exclusion and requires demonstration of the absence of a primary tumor elsewhere (10). The majority of primary thymic carcinomas, however, represent high-grade malignancies characterized by marked cytologic atypia, nuclear pleomorphism, necrosis and high mitotic activity; features that are generally absent in epithelioid hemangioendothelioma.
Table I: Epithelioid cell tumors of the Mediastinum.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Age</th>
<th>Histology</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical thymoma</td>
<td>40-60 yrs</td>
<td>- Sheets of epithelioid cells with sharp cell borders and large hyperchromatic nuclei with prominent nucleoli</td>
<td>- Epithelial cells: cytokeratin +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Low power lobulation; perivascular spaces</td>
<td>- Lymphocytes: immature T-cells (CD1a, CD3, CD45RO, CD99+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Rare mitotic figures; T-lymphocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Foci of squamous differentiation</td>
<td></td>
</tr>
<tr>
<td>Epithelial-rich thymoma</td>
<td>40-60 yrs</td>
<td>- Sheets of epithelioid cells with abundant cytoplasm and indistinct cell borders</td>
<td>- Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No cytologic atypia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Organotypical features same as above</td>
<td></td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>50-70 yrs</td>
<td>- Features of well-differentiated squamous cell carcinoma</td>
<td>- Epithelial cells: cytokeratin +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No lobulation or perivascular spaces</td>
<td>- Lymphocytes: type as B-cells or plasma cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- B-cells and plasma cells instead of T-lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Epithelioid hemangioendothelioma</td>
<td>30-60 yrs</td>
<td>- Sheets of epithelioid cells with abundant cytoplasm and vesicular nuclei</td>
<td>- Vascular markers + (CD31, CD34, FVIII-RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prominent intracytoplasmic vacuoles</td>
<td>- Cytokeratin + in some cases</td>
</tr>
<tr>
<td>Seminoma</td>
<td>25-40 yrs</td>
<td>- Sheets of large, discohesive cells with large nuclei and prominent nucleoli</td>
<td>- PLAP +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Dot-like paranuclear positivity for cytokeratin</td>
</tr>
<tr>
<td>Yolk sac tumor</td>
<td>30-50 yrs</td>
<td>- Sheets of epithelioid cells with enlarged nuclei; Intracytoplasmic and extracellular hyaline globules</td>
<td>- AFP +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Low-molecular weight cytokeratin +</td>
</tr>
</tbody>
</table>

Germ cell tumors of the mediastinum can also enter in the differential diagnosis of these lesions, in particular seminoma. Mediastinal seminoma is composed of a proliferation of large, epithelioid cells with irregular, hyperchromatic nuclei containing prominent nucleoli,
and surrounded by abundant clear or eosinophilic cytoplasm. The tumors are often infiltrated with numerous stromal lymphocytes and plasma cells, and may be associated with residual thymic epithelial elements including Hassall’s corpuscles (11, 12). The clue to the diagnosis lies in the discohesive nature of the cellular proliferation and the single, prominent, angulated eosinophilic nucleoli. Immunohistochemical stains are useful when there is the suspicion of seminoma by showing cytoplasmic positivity for placental-like alkaline phosphatase (PLAP) in the tumor cells (12). An important caveat is the fact that mediastinal seminomas, in contrast with their testicular counterparts, can be positive for low-molecular weight cytokeratin in up to 80% of cases (13). The pattern of staining can be helpful for differential diagnosis since seminoma cells are characterized by a very distinctive dot-like, paranuclear pattern of staining (13).

Yolk sac tumor of the mediastinum can also rarely enter in the differential diagnosis, particularly on small mediastinoscopic biopsies. Such tumors can show quite bland cytologic features and be composed of sheets of epithelioid cells with minimal atypia and very low mitotic activity that show strong cytoplasmic positivity for cytokeratin antibodies (14). The tumor cells, however, will also strongly react with antibodies to alpha-fetoprotein (AFP). In the majority of instances, the clinical presentation of the tumor (i.e., rapidly growing, bulky mediastinal mass in a young man with elevated AFP levels in serum) will raise the index of suspicion for this diagnosis.

References: