TUMORS AND TUMOR-LIKE CONDITIONS OF THE MEDIASTINUM

The Sheraton Seattle Hotel and Towers
Thursday, April 14, 8:30AM-12:00NOON

CASE HISTORIES

PRESENTERS:

JUAN ROSAI, M.D.
Chairman, Department of Pathology
Memorial Sloan-Kettering Cancer Center
Professor of Pathology
Cornell University Medical School
New York, New York

DAVID S. KLIMSTRA, M.D.
Assistant Attending Pathologist
Memorial Sloan-Kettering Cancer Center
Assistant Professor of Pathology
Cornell University Medical School
New York, New York

MODERATOR:

YAO SHI FU, M.D.
Professor of Pathology and
Chief of Surgical Pathology
University of California at Los Angeles Medical Center
Los Angeles, California

PLEASE BRING THIS PROTOCOL TO THE SEMINAR
Case Histories

Case 1: A 69 year old woman presented with shortness of breath. She was initially treated for pneumonia; however, a chest radiograph revealed a tumor in the right upper lung zone. Mediastinoscopy showed the tumor to arise from the anterior mediastinum. A frozen section diagnosis of "neuroendocrine tumor" was made, and the mass was excised. Grossly the 3cm tumor appeared encapsulated. On cut section the tissue was pink to tan and fleshy, with bands of white fibrous tissue dividing it into lobules.

Case 2: A 30 year old female first presented with cough and chest pain radiating to the back in 1986. A large anterior mediastinal mass was resected following a brief course of radiation therapy. The patient was well until 7/92 when she developed alopecia. A chest CT revealed local recurrence of tumor in the anterior mediastinum, which was re-excised. Grossly the tumor was firm and tan-white with a multinodular appearance. A portion of lung tissue was attached.

Case 3: A 59 year old male with a nine year history of progressive spinal/cerebellar degeneration of unclear etiology presented with shortness of breath. A chest radiograph revealed a 9cm left anterior mediastinal mass. A fine needle aspirate was non-diagnostic and resulted in a pneumothorax requiring chest tube placement. One month later the patient underwent median sternotomy with resection of the tumor. Grossly, the mass weighed 55 grams and measured 9x6.5x3.5cm. Cut sections revealed a tan to yellow, gritty, infiltrative tumor with cystic cavities measuring up to 2cm in diameter.

Case 4: A 42 year old male with a past history of excision of a parathyroid adenoma presented in 1990 with a sensation of "tightness" in the chest. There were no other symptoms. An anterior mediastinal mass was noted on chest radiograph. An open biopsy was performed and a diagnosis was established. The patient declined treatment for two years but then consented to resection when the mass was found to be increasing in size. Grossly, the tumor was 10cm in greatest diameter and covered by a thin capsule. The tissue was tan and soft with multiple small foci of necrosis and calcification.

Of note, the patient's brother had excisions of parathyroid and pituitary adenomas as well as a pancreatic endocrine tumor, his mother died of a widely metastatic endocrine neoplasm.

Case 5: A 75 year old male was noted to have a slowly growing mass in the left posterior mediastinum five years prior to surgery. However, a marked increase in size was noted and the tumor was resected. The patient was asymptomatic and laboratory studies were within normal limits. Grossly the tumor measured 20cm and weighed 1340 gm. It was partially encapsulated and consisted of firm, nodular white tissue with myxoid areas.
Case 6: The patient is a 72 year old white female who was noted to have an incidental mediastinal mass on a chest radiograph performed prior to repair of a rectocele in 1990. The patient refused further evaluation of the mass at that time, but presented in 1992 with increasing shortness of breath and anterior chest pain. On CT, the tumor measured 16cm and involved the anterior mediastinum and right hemithorax. Two components to the mass were identified, one of which had the appearance of adipose tissue. The tumor was resected uneventfully. Grossly the tumor was circumscribed and soft, with areas of yellow, fatty tissue alternating with more firm, white-tan, lobulated areas.

Case 7: A 62 year old man presented with a right supraclavicular mass which was found to be contiguous with a large anterior mediastinal mass. A biopsy was interpreted as neoplastic, possibly paraganglioma or thymoma. The tumor was resected in two pieces measuring 9cm and 11cm and weighing 320gm in aggregate. The cut section revealed multinodular yellow soft tumors with central hemorrhage and necrosis.

Case 8: A 66 year old man underwent a coronary artery bypass operation several years before presentation. On follow-up he was found to have a 5cm well-demarcated nodular mass exactly in the region when the pleura had been stripped to expose the internal mammary artery. Several 1-2mm nodules were also noted on the pleura adjacent to the main mass. The remainder of the pleura was unremarkable. There was no history of asbestos exposure or pleural effusion. The tumor was excised. Grossly the mass was brown-tan and homogeneous. There was no hemorrhage or necrosis.

Case 9: A 56 year old man presented in 2/92 with 2 months of cough, fatigue and dysphagia. Chest radiograph revealed a 13x10cm left anterior mediastinal mass. Biopsy via mediastinoscopy showed ectatic blood vessels in a fibrotic stroma, and the diagnosis of cancerous hemangioma was made. The patient received 2160 rads of radiation with no response. In 6/92 a more substantial biopsy was taken. At that time, the tumor filled the left chest with extension to the diaphragm. Grossly it appeared pink to gray with areas of necrosis.

Case 10: An 18 year old male, previously healthy, presented in 8/91 with fevers, night sweats, chest pain, and dyspnea on exersion. A left anterior mediastinal mass was detected on CT scan. The HCG level was 479 and the AFP level was 6900. A fine needle aspirate was performed, and malignant cells consistent with germ cell tumor were found. The patient received six cycles of VIP chemotherapy which was completed on 12/13/91. The HCG and AFP levels returned to normal, but there was no radiographic change in the appearance of the tumor. On 1/20/92, a transverse sternotomy and bilateral thoracotomies were performed, with resection of the tumor. Grossly, the 320 gm tumor measured 10x9x6.3cm and was circumscribed, lobulated, and surrounded by a thin capsule. Cut sections revealed numerous small cystic spaces within a tan, hemorrhagic tumor with focal myxoid areas and calcifications. The cysts contained thick mucinous material.
## Tumor and Tumor-Like Conditions of the Mediastinum

### ASCP Spring Seminar

<table>
<thead>
<tr>
<th>Case</th>
<th>SP#</th>
<th>Diagnosis</th>
<th>Presentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S93-08264</td>
<td>Invasive thymoma (rosettes)</td>
<td>JR</td>
</tr>
<tr>
<td>2</td>
<td>S92-18822</td>
<td>Malignant thymoma (type 1.5)</td>
<td>JR</td>
</tr>
<tr>
<td>3</td>
<td>S91-25688</td>
<td>Mucoepidermoid carcinoma</td>
<td>DK</td>
</tr>
<tr>
<td>4</td>
<td>S92-22874</td>
<td>Carcinoid</td>
<td>DK</td>
</tr>
<tr>
<td>5</td>
<td>S93-15496</td>
<td>Solitary fibrous tumor</td>
<td>JR</td>
</tr>
<tr>
<td>6</td>
<td>S92-17850</td>
<td>Thymoliposarcoma</td>
<td>DK</td>
</tr>
<tr>
<td>7</td>
<td>S92-21070</td>
<td>Reticulum cell sarcoma</td>
<td>JR</td>
</tr>
<tr>
<td>8</td>
<td>S92-06902</td>
<td>Mesothelial proliferation</td>
<td>DK</td>
</tr>
<tr>
<td>9</td>
<td>S92-14367</td>
<td>Germ cell tumor with sarcoma</td>
<td>JR</td>
</tr>
<tr>
<td>10</td>
<td>S92-01566</td>
<td>Teratoma with chemotherapy effect</td>
<td>DK</td>
</tr>
</tbody>
</table>
CASE #1

CLINICAL HISTORY:

A 69 year old woman presented with shortness of breath. She was initially treated for pneumonia; however, a chest radiograph revealed a tumor in the right upper lung zone. Mediastinoscopy showed the tumor to arise from the anterior mediastinum. A frozen section diagnosis of "neuroendocrine tumor" was made, and the mass was excised.

GROSS DESCRIPTION:

The 3cm tumor appeared encapsulated. On cut section the tissue was pink to tan and fleshy, with bands of white fibrous tissue dividing it into lobules.

HISTOLOGICAL FEATURES:

This mediastinal neoplasm represents a thymoma exhibiting a well-vascularized pattern and a profusion of rosettes. There is a great predominance of epithelial cells over the lymphocytes, the former having a shape ranging from round to oval to spindle. The tumor capsule is violated in several areas by tumor growth, and there are several nodules of tumor located immediately outside in the adjacent mediastinal fat.

COMMENT:

This thymoma is designated in the various classifications as spindle, rosette-making, or medullary. Because of its capsular invasion, it should be regarded as a malignant thymoma type I and classified as stage II (microscopic invasion into the capsule) in the Masaoka's system. This translates as a T2N0M0 in the recently proposed staging system for this neoplasm. In our opinion, the tumor represented by this case is a neoplasm of nonfunctional, post-mature thymic epithelial cells which do not match phenotypically either medullary or cortical cells, but rather those of the effete epithelial cells seen in the involuted thymus of adult life. This type of thymoma is characterized by the presence of rosettes, gland-like spaces, foci of storiform arrangement, and scantiness or absence of lymphocytes. These lymphocytes are usually of mature T-cell type, i.e., different phenotypically to those present in other thymomas, which are characterized by a phenotype corresponding to that of cortical thymocytes. Nearly all cases of the thymoma type represented by the Seminar case are encapsulated (stage I) or only minimally invasive (stage II). As a result the prognosis following excision is excellent.

Overall, about 70 to 80 percent of thymomas are encapsulated. Direct local invasion (first into the capsule and mediastinal fat, later into adjacent structures, such as lung) or implants into the pleural or pericardial surfaces are considerably more common events in thymoma than distant metastases. When local invasion is extensive, it is already apparent to the surgeon at the time of the thoracotomy. It is therefore important for the pathologist to know the surgical findings, while remembering that fibrous adhesions resulting from secondary inflammatory, necrosis, and multilocular cystic changes can give the surgeon the false impression that the tumor is invasive. The term "minimal invasion" refers to the findings in this case, i.e., complete capsular breaks or tumor islands in the mediastinal fat. Presence of large nerves surrounded by tumor also represent indirect evidence of invasion.

In regard to the rosettes which are so prominently displayed by this tumor, it is important to distinguish them from the rosette-like structures seen in thymic carcinoid. The latter, in contrast to those of thymoma, have a well-defined lumen and therefore represent evidence of glandular differentiation. The type of thymoma represented by the Seminar case is very rarely associated.
with myasthenia gravis or any other of the paraneoplastic syndromes that have been reported with thymoma as a group. In regard to the classification scheme, we would like to point out that although this thymoma is designated in some classification schemes as "medullary" (implying a histogenetic relationship with the normal medulla of the thymus), (9) no consistent relation has yet been found between the proposed types of thymoma (including this one) and the known phenotypes of normal thymic epithelial cells. (1,2,4,11) This criticism notwithstanding, credit should be given to the authors of recent publications of the subject for increasing our awareness of the statistical relationship between the cytoarchitectural features of thymoma and behavior, particularly in regard to the fact that tumors composed exclusively or predominantly of bland-appearing spindle/oval cells are nearly always encapsulated and associated with an excellent prognosis, and that in tumors composed of round/polygonal epithelial cells, aggressiveness is directly related both to the numerical predominance of epithelial cells over the lymphocytes and to the presence and degree of atypia in those epithelial cells. (9)

DIAGNOSIS:

MALIGNANT THYMOMA TYPE I, SPINDLE ("MEDULLARY") TYPE

REFERENCES:


CASE #2

CLINICAL HISTORY:

A 30 year old female first presented with cough and chest pain radiating to the back in 1986. A large anterior mediastinal mass was resected following a brief course of radiation therapy. The patient was well until 7/92 when she developed alopecia. A chest CT revealed local recurrence of tumor in the anterior mediastinum, which was re-excised.

GROSS DESCRIPTION:

The tumor was firm and tan-white, with a multinodular appearance. A portion of lung tissue was attached.

HISTOLOGICAL FEATURES:

This thymic neoplasm is clearly malignant by virtue of the fact that it is growing outside its original confines and extending into lung. However, it retains the classical cytoarchitectural features of a thymoma, and in all likelihood the lymphocytes present in it are CD1 positive, immature cortical thymocytes. The neoplastic epithelial cells have in areas the typical appearance of those described in the thymoma type variously designated as epithelial or cortical. In others areas, they show marked cytologic atypia, associated with squamous differentiation and mitotic activity.

COMMENT:

The interpretation and description of this thymic neoplasm might create some problems for those authors who like to draw a sharp separation between thymoma and thymic carcinoma, because it would be regarded as a thymoma on the basis of the architectural features and as a thymic carcinoma on the basis of the cytologic atypia. It seems to us that this case is a perfect demonstration of the existence of thymic neoplasms that fall in between those two extremes. In this regard, the recent proposal to add the category of "well-differentiated thymic carcinoma" for a tumor type that is included among the thymomas in all publications on the subject (a fact that may not be immediately apparent to all readers) may not be particularly useful. From the point of view of staging, the present neoplasm corresponds to a stage III in Masaoka's system (gross invasion into a neighboring organ) and as a T3N0M0 in the recently proposed TNM staging system. As already stated, direct local invasion or implants are considerably more common events in thymoma than distant metastases. The latter, which are exceptional, have been documented in mediastinal and cervical lymph nodes, lung, liver, bone (particularly spine), ovary (we have seen three examples), and other sites. Usually they develop months or years after the invasive thymoma has been detected and treated; sometimes they are noted at presentation, and exceptionally represent the first clinical manifestation of the disease.

The treatment of malignant thymoma associated with gross invasion or implants usually consists in a combination of excision and radiation therapy. When distant metastases are present, chemotherapy has been added; combination regimes containing cis-platinum have shown the best results. Conventional thymic carcinoma of either squamous or lymphoepithelioma-like type are also treated with surgery plus radiation therapy, with chemotherapy added in cases of massive local disease or distant spread. The prognosis of fully encapsulated thymoma following surgical excision is excellent regardless of microscopic type. The prognosis of invasive thymoma depends greatly on the completeness of the original excision. It also correlates with the degree of invasiveness, a fact that has been taken into account for the various staging systems for these tumors. The
prognosis drops significantly for the tumors showing gross invasion or implants and even more so for the few cases associated with distant metastases. The prognosis of thymic carcinoma depends a great deal on the microscopic subtype. It is very aggressive for the nonkeratinizing carcinoma (including the lymphoepithelioma-like tumors), sarcomatoid carcinoma, clear-cell carcinoma, and undifferentiated (anaplastic) carcinoma; intermediate for squamous cell carcinoma; and relatively indolent for the rare mucoepidermoid and basaloid carcinomas.\(^{(7,8)}\)

**DIAGNOSIS:**

**MALIGNANT THYMOMA TYPE 1.5**

**REFERENCES:**


CASE #3

CLINICAL HISTORY:

A 59 year old male with a nine year history of progressive spinal/cerebellar degeneration of unclear etiology presented with shortness of breath. A chest radiograph revealed a 9cm left anterior mediastinal mass. A fine needle aspirate was non-diagnostic and resulted in a pneumothorax requiring chest tube placement. One month later the patient underwent median sternotomy with resection of the tumor.

GROSS DESCRIPTION:

The mass weighed 55 grams and measured 9x6.5x3.5cm. Cut sections revealed a tan to yellow, gritty, infiltrative tumor with cystic cavities measuring up to 2cm in diameter.

HISTOLOGICAL FEATURES:

The tumor cells are arranged in variably sized nests separated by bands of focally cellular, focally hyalinized stroma. Scattered throughout the tumor are cystic structures which are lined by cuboidal to squamous epithelium with interspersed goblet cells. The more solid areas show similar cell types, with an admixture of clear cells and intermediate cells. There is accumulation of extracellular mucin which in areas extends into the stromal tissue, resulting in a fibro-inflammatory reaction. Mucicarmine staining highlights the large goblet cell component of this neoplasm. Cytologically, the tumor is well-differentiated, with minimal nuclear pleomorphism.

COMMENT:

These features are diagnostic of mucoepidermoid carcinoma of the thymus. Only three cases of this tumor have been reported;\(^{(4,6,7)}\) it is one of the many types of thymic carcinoma (others being well-differentiated squamous cell carcinoma, basaloid carcinoma, lymphoepithelioma-like carcinoma, neuroendocrine carcinoma, anaplastic carcinoma, sarcomatoid carcinoma, and clear cell carcinoma).\(^{(1,2,6,9)}\) Histologically, the tumor is essentially indistinguishable from mucoepidermoid carcinoma of the salivary glands; therefore, the possibility of metastasis should always be considered. The reported cases have occurred in adult patients and have pursued an indolent clinical course, belonging to the low-grade histology group of thymic carcinomas defined by Suster and Rosai,\(^{(6)}\) which also includes well-differentiated squamous cell carcinoma and basaloid carcinoma. The histogenesis of mucoepidermoid carcinoma in the thymus is not entirely clear. The possibility that these tumors arise either from aberrant salivary tissue in mediastinal teratomas or from congenital cysts of the thymus (such as bronchogenic cysts) has been suggested, and one reported case did coexist with a thymic cyst lined by respiratory epithelium.\(^{(7)}\) An alternative (and probably more likely) explanation is that mucoepidermoid carcinomas arise from the thymic epithelium. It is well known that mucinous metaplasia of the thymic epithelium can occur, and cases of multilocular thymic cyst\(^{(5)}\) containing goblet cells do recur.

Entities to be considered in the differential diagnosis are primarily epithelial thymomas containing gland-like spaces, mediastinal teratomas containing glandular and squamous elements, and high-grade thymic carcinomas showing squamous and glandular differentiation (adenosquamous carcinoma).\(^{(2,3,8)}\)

DIAGNOSIS:

MUÇOEPIDERMOID CARCINOMA OF THE THYMUS
REFERENCES:


CASE #4

CLINICAL HISTORY:

A 42 year old male with a past history of excision of a parathyroid adenoma presented in 1990 with a sensation of “tightness” in the chest. There were no other symptoms. An anterior mediastinal mass was noted on chest radiograph. The lungs were free of masses. An open biopsy was performed and a diagnosis was established. The patient declined treatment for two years but then consented to resection when the mass was found to be increasing in size.

Of note, the patient’s brother had excisions of parathyroid and pituitary adenomas as well as a pancreatic endocrine tumor, and his mother died of a widely metastatic endocrine neoplasm.

GROSS DESCRIPTION:

The tumor was 10cm in greatest diameter and covered by a thin capsule. The tissue was tan and soft with multiple small foci of necrosis and calcification. A portion of lung was densely adherent to one aspect, and lobulated adipose tissue suggestive of residual thymus gland was present elsewhere.

HISTOLOGICAL FEATURES:

The tumor is very cellular, with solid sheets and nests of small cells separated by a scanty but well-vascularized stroma. In areas the nesting growth pattern is pronounced. The central portions of the nests exhibit comedo-type necrosis with frequent calcification. Within the nests (and in the more solid areas) the cells are arranged in rosettes with central lumina. At the periphery of the tumor there is infiltration into the surrounding adipose tissue, lung, and residual thymus; in these areas the cells are growing individually and in thin trabeculae. Cytologically, the cells are uniform with minimal amphophilic cytoplasm. Nuclei are round to oval and lack pleomorphism. The chromatin is dispersed and nucleoli are inconspicuous. Mitoses are easily found and range from 10-15 per 10 high power fields. Vascular invasion is present.

Immunohistochemical staining reveals the tumor cells to be positive for keratin (Cam 5.2), chromogranin, synaptophysin, and neuron specific enolase. Stains for S100 protein, neurofilaments, and parathyroid hormone are negative.

COMMENT:

This tumor is clearly an endocrine neoplasm, and the clinical presentation and gross and microscopic features establish it as a thymic primary, i.e., thymic carcinoid. Although the features of thymic carcinoids overlap somewhat those of pulmonary carcinoid tumors, endocrine neoplasms including carcinoid and small cell carcinoma have been accepted to arise primarily within the thymus,[7,16,19] although these tumors were probably classified as thymomas until 25 years ago. The cells of origin are presumably the small population of endocrine cells which have been observed within the thymuses of animals[3,5] and humans[17].

Thymic carcinoids typically arise in young adults (mean = 45), with males being more commonly affected[16]. Although most of the patients present with symptoms related only to the mass itself, approximately one third suffer from paraneoplastic endocrinopathies, most commonly Cushing’s syndrome[1,4,8] due to ACTH secretion by the tumor. In addition, cases of thymic carcinoids associated with MEN I have been reported[10,14]; the tumor in the seminar case clearly belongs to this group. Rare cases associated with MEN II have also been described[11].
The histologic features of the seminar case are typical, although trabecular formations may be more pronounced. Of note, the presence of "aggressive" endocrine features (such as necrosis and increased mitoses) is common, although nuclear pleomorphism is generally not marked. Some histologic variants have been described, including spindle cell carcinoid and patterns mimicking medullary thyroid carcinoma. Immunohistochemically the tumors are positive for keratin and general endocrine markers such as chromogranin, synaptophysin, and NSE. Peptides such as ACTH, somatostatin, cholecystokinin, and serotonin may also be detected.

In comparison with pulmonary carcinoids, thymic carcinoid tumor is an aggressive neoplasm. Local invasion is common, up to 75% of patients develop metastases, and death from tumor is not infrequent, usually within a few years. Those tumors occurring in the context of MEN may be more aggressive.

It is usually not difficult to exclude the possibility of mediastinal metastasis from a pulmonary primary on clinical grounds. Most metastasizing pulmonary carcinoid tumors are detectable radiographically (although at least one case of a metastasizing pulmonary "tumorlet" has been reported), and if bronchoscopic examination of the bronchial tree has also failed to identify a pulmonary tumor, an anterior mediastinal carcinoid tumor can be regarded as most likely thymic in origin. In addition, there are some histologic differences between thymic and pulmonary carcinoids. The former tumors often have larger nests of cells, and the central necrosis and calcification is characteristic. In addition, rosette formation is more common in thymic primaries. Finally, the general appearance of thymic carcinoids is that of a more aggressive endocrine neoplasm than the typical pulmonary carcinoid tumor. In fact, the term "atypical carcinoid" would probably better suit thymic carcinoids, given the presence of mitoses and necrosis and the relatively aggressive behavior.

Small cell carcinomas within the anterior mediastinum may be more difficult to establish as thymic primaries because of the well-known propensity of pulmonary small cell carcinomas to metastasize widely while still very small. Thus, careful radiographic and bronchoscopic evaluation of the lungs must be performed before the diagnosis of primary thymic small cell carcinoma can be confirmed.

In addition to metastases from the lung (or other sites), tumors in the differential diagnosis include other primary endocrine tumors of the mediastinum. Tumors (and hyperplasias) of parathyroid glands are encountered in the mediastinum and may be associated with the thymus, a not unexpected phenomenon given the common embryologic origin of the two structures. While hyperplasia and adenoma are by far the most commonly occurring conditions, cases of primary mediastinal parathyroid carcinoma have been reported as well. Parathyroid lesions with chief cell predominance are most likely to be confused with thymic carcinoids. The clinical history of hypercalcemia and immunohistochemical detection of parathyroid hormone can confirm the diagnosis. Paragangliomas also occur in the mediastinum. Prominence of a "zellballen" growth pattern, pleomorphism of the nuclei and the lack of necrosis and mitotic activity are features of paraganglioma, and immunohistochemistry may be helpful as well. While both paragangliomas and carcinoids are positive for chromogranin, paragangliomas lack keratin staining and may express neurofilaments. The finding of abundant S-100 protein-positive sustentacular cells around the nests of tumor cells also supports the diagnosis of paraganglioma, although similar cells have occasionally been seen in carcinoid tumors. Nonendocrine neoplasms can also simulate thymic carcinoid. The rosette-like patterns which may be seen in thymomas may cause confusion with thymic carcinoid, and spindle cell carcinoids may be mistaken for spindle cell thymomas. In addition to the lack of immunohistochemical staining for endocrine markers, thymomas typically lack necrosis and relatively abundant mitoses, and scattered lymphocytes are usually present (at
least focally). In some cases, thymic carcinoids may also mimic germ cell tumors or lymphomas. Immunohistochemistry is again of great utility in these distinctions.

**DIAGNOSIS:**

**THYMIC CARCINOID TUMOR**

**REFERENCES:**


CASE #5

CLINICAL HISTORY:
A 75 year old male was noted to have a slowly growing mass in the left posterior mediastinum five years prior to surgery. However, a marked increase in size was noted and the tumor was resected. The patient was asymptomatic and laboratory studies were within normal limits.

GROSS DESCRIPTION:
The tumor measured 20cm and weighed 1340 gm. It was partially encapsulated and consisted of firm, nodular white tissue with myxoid areas.

HISTOLOGICAL FEATURES:
This mediastinal neoplasm is a typical example of the entity currently known as solitary fibrous tumor. It is possible that some of these tumors grow into the mediastinum from the medial pleura, but we think that most originate from the mediastinal (including thymic) stroma. Their microscopic appearance and immunohistochemical profile are similar to those of their pleural counterparts, but a higher proportion of their reported cases have run an aggressive clinical course. The most striking microscopic feature is the alternation of hyper- and hypocellular foci, both of them composed of oval to spindle cells growing in ill-defined fascicles and separated by keloid-type collagen. Cellularity can be very high, but there is usually little pleomorphism. Necrosis and mitotic activity can be seen and represent two of the most important criteria for predicting aggressive behavior.

COMMENT:
Although this tumor was regarded for many years as originating from mesothelial cells on the basis of tissue culture studies and designated as solitary fibrous tumor, it has become increasingly apparent that it is instead made up of fibroblasts/myofibroblasts having phenotypical features equivalent to those of submesothelial connective tissue cells. The tumor cells are probably responsible for the large amounts of collagen deposited in these tumors. Immunohistochemically, they are strongly reactive for vimentin, focally and inconstantly positive for actin, and negative for desmin, S100 protein, and keratin. We have recently found that they also show a consistent, strong, and widespread positivity for CD34, a feature that they also share with dermatofibrosarcoma protuberans, other "fibrohistiocytic" tumors, some peripheral nerve neoplasms, endothelial tumors, and epithelioid sarcoma.

Other locations in which this neoplasm has been reported (in addition to pleura and mediastinum) include peritoneum, liver, lung (without pleural connection), upper respiratory tract and orbit. There is also a remarkable similarity between this entity as reported in those sites and at least some cases of the tumor of the male and female breast known as myofibroblastoma (including the CD34 positivity that we have documented in some of these cases). Some examples of these solitary fibrous tumors (especially when large) are associated with tumor-related hypoglycemia, which promptly disappears following removal of the neoplasm. Practically all of the mesenchymal tumors that we have had the opportunity to review that were associated with this paraneoplastic syndrome have belonged to this tumor type, although many have been diagnosed or reported as fibrosarcoma, leiomyosarcoma, or hemangiopericytoma. The hypoglycemia has been found to be due to the secretion by the tumor of an insulin-like growth factor II.
DIAGNOSIS:
SOLITARY FIBROUS TUMOR

REFERENCES:


CASE #6

CLINICAL HISTORY:

The patient is a 72 year old white female who was noted to have an incidental mediastinal mass on a chest radiograph performed prior to repair of a rectocele in 1990. The patient refused further evaluation of the mass at that time, but presented in 1992 with increasing shortness of breath and anterior chest pain. On CT, the tumor measured 16cm and involved the anterior mediastinum and right hemithorax. Two components to the mass were identified, one of which had the appearance of adipose tissue. The tumor was resected uneventfully.

GROSS DESCRIPTION:

The tumor was circumscribed and soft, with areas of yellow, fatty tissue alternating with more firm, white-tan, lobulated areas.

HISTOLOGICAL FEATURES:

At low power the tumor has a geographic appearance. Cords and nests of thymic tissue are separated by bands of fibroadipose tissue with focal sclerosis. The thymic tissue contains abundant lymphocytic in many areas, and scattered Hassell's corpuscles can be seen. Focally the lymphocytes are absent, and the thymic tissue is limited to thin strips of epithelial cells lacking keratinization. The fibroadipose tissue contains large, atypical cells which are most numerous in the more sclerotic regions. Focally the nuclear atypia involves the adipocytes, and scattered multivacuolated lipoblasts are present. In some areas the thymic tissue is absent, and the fatty component becomes more myxoid. Spindle cells predominate elsewhere. Atypical cells are more abundant in these regions, although the lesion retains a low-grade appearance throughout, lacking hypercellularity, increased mitoses, and necrosis.

COMMENT:

This tumor contains elements of benign thymic tissue (both the epithelial and lymphocytic components) and well differentiated liposarcoma (focally sclerosing). The abundance of thymic tissue within the lesion and the intimate admixture of the two components suggests that the malignant component not only arose within the thymus gland but induced a proliferation of the thymic epithelium as well. Tumors with this appearance have been referred to as "thymoliposarcomas", in analogy with their benign counterpart, the thymolipoma. Only two such cases have been described; both appeared to arise de novo, having no evidence of a pre-existing thymolipoma.

Although malignant lipomatous tumors with this distinctive appearance are very uncommon, liposarcomas of the thymus and anterior mediastinum are probably the most frequent mesenchymal tumors of that region. Over 80 cases of mediastinal liposarcoma have been reported, with the majority occurring in the antero-superior mediastinum. Some can be grossly or microscopically proven to have arisen within the thymus (25% of anterior mediastinal liposarcomas), but in these cases the thymic tissue consists only of remnants compressed around the periphery of the tumor. It is possible that an even greater percentage of anterior mediastinal liposarcomas arise within the thymus, and some of the larger tumors may completely replace the gland.

 Mediastinal liposarcomas occur over a wide age range, including children and elderly adults; the mean age is 42 years. Males are more commonly affected. Presenting symptoms are often non-specific but may include pain, respiratory difficulty, and superior vena cava syndrome.
The tumors may reach very large sizes (up to 40.0 cm), with extension into the thoracic cavities. Grossly, the appearance is similar to that of liposarcomas occurring elsewhere and depends upon the histologic type.

The histologic features of mediastinal liposarcomas are similar to those of liposarcomas occurring in the retroperitoneum or extremities. All histologic types occur (well differentiated lipoma-like and sclerosing, myxoid, round cell, and pleomorphic), with most cases being low grade (89%). The well differentiated types constitute 57%, while 32% of cases are the myxoid type. One interesting feature of the sclerosing variant is the frequent presence of large dense aggregates of lymphoid cells which occasionally contain follicles. Within this background, the scattered atypical tumor cells may easily be mistaken for the Reed-Sternberg cells of nodular sclerosis Hodgkin's disease. These aggregates probably represent reactive lymphocytic components rather than residual thymic lymphocytes, since an equal admixture of B-cells and T-cells is found.

The clinical course of mediastinal liposarcomas parallels that of similar tumors within the retroperitoneum. Patients with low grade tumors experience repeated recurrences and usually die of local disease, often after many years. The rare high grade liposarcomas are capable of distant metastases as well as locally aggressive behavior. Treatment has largely been surgical, and the multilobulated growth pattern of these tumors make complete excision difficult. Chemotherapy and radiation therapy have been employed in some cases, but there are inadequate data to assess their efficacy.

One of the entities in the differential diagnosis (especially in case of thymoliposarcoma) is thymolipoma. In these tumors, there is intimate admixture of thymic elements with mature adipose tissue, and no malignant cells are seen in the stromal component. In addition spindle cell elements, sclerosis, and myxoid areas are not seen. Thymolipomas are considered completely benign; cases associated with myasthenia gravis and aplastic anemia have been reported. The possibility of lipomas occurring in the mediastinum must also be considered, but (in the retroperitoneum) the minimal degree of atypia which may be present in well differentiated, lipoma-like liposarcomas suggests that the diagnosis of lipoma must be made with great caution. Multivacuolated cells, cytologic atypia, or areas of sclerosis should raise suspicions that cells diagnostic of liposarcoma are likely to be present. The differential diagnosis also includes other sarcomas which can occur in the mediastinum. MFH, leiomyosarcoma, chondrosarcoma, angiosarcoma, and osteosarcoma have all been described, and each has distinctive histologic (and possibly immunohistochemical) features while lacking lipoblasts. The possibility that a mediastinal sarcoma has arisen from an underlying teratoma must be considered; this transformation appears to be more frequent in mediastinal germ cell tumors than in those occurring elsewhere. Malignant peripheral nerve sheath tumors also occur, usually in the posterior mediastinum. Of course, the possibilities of sarcomatoid carcinoma (of thymic or other origin) or sarcomatoid epithelial mesothelioma must be considered for high grade spindle cell neoplasms before the diagnosis of sarcoma can be confirmed. Solitary fibrous tumors can also involve the mediastinum and may mimic the more sclerotic areas of liposarcomas. The recently described positivity of solitary fibrous tumors for CD34 may be helpful in this differential.

**DIAGNOSIS:**

**THYMIC LIPOSARCOMA ("THYMOLIPOSARCOMA")**

**REFERENCES:**


CASE #7

CLINICAL HISTORY:

A 62 year old man presented with a right supraclavicular mass which was found to be contiguous with a large anterior mediastinal mass. A biopsy was interpreted as neoplastic, possibly paraganglioma or thymoma. The tumor was resected in two pieces measuring 9cm and 11cm and weighing 320gm in aggregate.

GROSS DESCRIPTION:

The cut section revealed multinodular yellow soft tumors with central hemorrhage and necrosis.

HISTOLOGICAL FEATURES:

This mediastinal tumor seems to be arising from a lymph node, judging from the fact that large amounts of residual lymph node structures are present in some of the sections. It is in these areas that the relationship between the tumor cells and the non-neoplastic lymphoid component can be better appreciated. The tumor cells are represented by plump elements with large vesicular nuclei and prominent nuclei which are arranged individually or in small clusters around the normal lymphoid cells. In other areas, they form larger clusters that eventually result in an obliteration of the lymph node architecture. In these solid areas, the tumor cells also acquire a greater degree of atypicality, with nuclear hyperchromasia and mitotic activity. Focally, the close intermingling of neoplastic cells and lymphocytes is reminiscent of that seen in thymoma, to the point that some areas would be difficult to distinguish from some in Seminar Case 2. Immunohistochemically, the tumor cells of this case are negative for all epithelial and endothelial markers. They are instead positive for vimentin and CD21. The combination of cytological, architectural, and immunohistochemical features strongly suggest that this lesion represents a neoplasm of true reticular cells, specifically those associated with follicular B cell zones, which have been variously referred to as dendritic reticular cells and dendritic follicular cells.

COMMENT:

The fact that there is a family of cells related to the immune system that have as a main function that of presenting antigen to the lymphoid elements is now widely accepted. The original term "reticulum cell" derives from the fact that these cells have elongated cytoplasmic processes joining each other and resulting in the formation of a network ("reticulum"). Later on, this was also linked to the association with (and presumed formation of) reticulin fibers by these cells. The old concept of reticulum cell sarcoma stems from the belief that the tumors so designated originated from this segment of the immune system. Although it was subsequently demonstrated that the large majority of tumors diagnosed in the past as reticulum cell sarcomas represent large-cell lymphomas of either B or T cell type, there is now good evidence that true reticulum cell sarcomas do indeed exist, and that some of them have the phenotype of dendritic cells whereas others have the phenotype of interdigitating reticulum cells. The diagnosis is based on a combination of features which include conventional morphology, enzyme histochemistry, electron microscopy, and immunohistochemistry. The majority of the dendritic reticulum cell tumors that we have seen have involved cervical lymph nodes, but cases of this entity have also been reported in extranodal sites, such as oral cavity and skin. At the electron microscopic level, the most important distinguishing feature of these cells is the presence of long cytoplasmic prolongations and the fact that these prolongations are joined by complex desmosomes. As a matter of fact, the dendritic reticulum cell is the only normal element in lymph nodes that contains complex intercellular junctions of this type.
Immunohistochemically, the most important markers are R4/23 (which can be demonstrated only in frozen sections), KiM4, CD21, and CD35.1,5,7 S100 protein reactivity is inconstant. In the normal situation, the latter reactivity is associated with interdigitating rather then dendritic reticulum cells, but in the neoplastic counterparts the results with this marker have been rather erratic.9

Dendritic reticulum cell tumor is a low-grade malignancy which is characterized by a tendency to local recurrence and eventually (in some cases) distant spread. There is a tendency for progressive pleomorphism, increased mitotic activity, and necrosis in the recurrent lesions. In the later stages, it may impossible to distinguish this tumor from an anaplastic large cell lymphoma or a non-lymphoid malignancy.4 At the H&E level, one of the most important distinguishing features is the close intermingling of tumor cells and lymphocytes. This feature, plus the fact that the tumor cells have nuclei of predominantly oval shape and vesicular appearance are responsible for some cases of this entity having been misdiagnosed in the past as ectopic cervical thymomas.

**DIAGNOSIS:**

**CONSISTENT WITH TRUE RETICULUM CELL TUMOR**

**REFERENCES:**


CASE #8

CLINICAL HISTORY:

A 66 year old man underwent a coronary artery bypass operation several years before presentation. On follow-up he was found to have a 5 cm well-demarcated nodular mass exactly in the region when the pleura had been stripped to expose the internal mammary artery. Several 1-2 mm nodules were also noted on the pleura adjacent to the main mass. The remainder of the pleura was unremarkable. There was no history of asbestos exposure or pleural effusion. The tumor was excised.

GROSS DESCRIPTION:

The mass was brown-tan and homogeneous. There was no hemorrhage or necrosis.

HISTOLOGICAL FEATURES:

The tumor consists of uniform, epithelial-appearing cells with minimal stroma within the lesion. Numerous islands of lymphocytes and plasma cells are present. Architecturally the cells are arranged in solid nests and sheets. Branching cleft-like spaces are present between groups of cells, and the cells projecting into these spaces have a "hob-nailed" appearance. Scattered papillary and tubular formations are present. In many areas the cells appear somewhat dis cohesive. On high power, individual cells are separated from their neighbors by clear spaces. The nuclei are uniform with mild atypia, although prominent nucleoli are conspicuous. Mitoses are detectable but not frequent. At the periphery the tumor is partially surrounded by a fibrous pseudocapsule, although focally nests of cells have invaded into the adjacent fat.

Immunohistochemically the tumor cells are diffusely positive for keratin (Cam 5.2 and AE1) but stain negatively for CEA, LeuM1, and B72.3. No mucin is detectable. By electron microscopy the cells have the characteristics of mesothelial cells, with numerous long microvilli.

COMMENT:

The pathologic features of this tumor are clearly those of a mesothelial proliferation. Histologically, the growth pattern (with sheets, papillae, and tubules) and cytologic features are typical, the immunohistochemical profile and lack of mucin are characteristic, and the ultrastructural appearance completes the picture. The fundamental questions about this tumor are twofold: first, is it a neoplastic proliferation, and second, if neoplastic, is it benign or malignant.

Evidence to suggest that this tumor may be a reactive proliferation exists, and arguments could also be made that it is a malignant neoplasm; however, the concept of a benign neoplastic proliferation of mesothelial cells is not well accepted to occur in the pleural cavity. Indeed, grading of epithelial mesotheliomas has not even been worthwhile, since well differentiated examples usually pursue the same rapidly aggressive course as their poorly differentiated counterparts. Thus, once a mesothelial proliferation in the pleura is determined to be neoplastic, it is by definition malignant. Benign mesothelial tumors do occur in the peritoneum (especially the pelvis), but these tumors are characteristic clinicopathologic entities (adenomatoid tumors and multicystic mesotheliomas) and do not share histologic features with the seminar case. The only benign tumor of the pleura to be classified as a mesothelioma is the localized (or solitary) fibrous "mesothelioma". This tumor is now known to be of mesenchymal rather than mesothelial derivation. Under the name of solitary fibrous tumor, it (along with its malignant counterpart, which is a true sarcoma) is now classified separately from true mesothelial neoplasms, and should especially be distinguished
from sarcomatoid mesotheliomas, which are epithelial neoplasms with a sarcomatoid growth pattern (analogous to sarcomatoid carcinomas of many organs).

If this tumor is a reactive proliferation, it would be regarded as an (extreme) example of nodular mesothelial hyperplasia. This condition was first described as an incidental finding in hernia sacs, but similar proliferations can be seen in other mesothelial-lined areas. In fact, the mesothelial lining of the pericardium is well known to undergo florid reactive proliferation, to the point that the diagnosis of primary pericardial mesothelioma should be made with great caution. The features of the current case which suggest a reactive proliferation include the relative lack of atypia and mitotic activity (indeed, nodular mesothelial hyperplasia may contain more abundant mitoses than the seminar case), the localized nature of the tumor, and the temporal association of the mass with the previous surgery in that area. Recently there has been recognition that manipulation of the tissue in the region of the heart and pericardium may result in the proliferation of mesothelial and other cells, resulting in a lesion which may resemble mesothelial neoplasms (i.e., mesothelioma) or other tumors. The similarity of these proliferations to epithelioid hemangioma has been noted, but immunohistochemical positivity for keratin (with negative staining for factor VIII) points toward their mesothelial nature. Other investigators have noted the admixture of monocytes with the mesothelial cells in these lesions and have suggested the term "mesothelial/monocytic incidental cardiac excresences" or "cardiac MICE"; proliferation reactive to cardiac catheterization was favored. Similar tissue fragments were also found in the suction tips of cardiac bypass pump filters, suggesting that the tumors are not even proliferative lesions but rather artifactual accumulations of mesothelial cells and other debris mechanically removed during surgery or other manipulation. Another point is that mesothelial cells may be found as incidental lymph node inclusions in the mediastinum, another non-neoplastic phenomenon which could be confused with mesothelioma. Thus, there is ample precedent for reactive mesothelial proliferations in this region, especially following surgery.

Despite these points, there are many features of the lesion in question which differ from the reactive proliferations mentioned. This tumor arose three years after surgery. Although continued proliferation of a cardiac "MICE" could be considered, this is clearly not an "incidental" lesion. No monocyte component was present, and the proliferation had a monotonous appearance. Although the histologic characteristics are not dissimilar to those of nodular mesothelial hyperplasia, the size of the lesion far exceeds any examples we have seen. Also, there was focal invasion into surrounding tissues as well as several additional pleural nodules noted at surgery (not biopsied). Thus, the conservative interpretation would have to be that this tumor represents an early (i.e., currently localized) malignant epithelial mesothelioma which would be expected to progress to diffuse pleural involvement with time. The primary location in the mediastinum would be unusual but has been reported.

Obviously, one would have to consider thymoma in the differential diagnosis of this lesion, although the growth pattern is highly suggestive of mesothelial cells, and the architectural features of thymoma are lacking. The opposite phenomenon (i.e., the pleural growth of thymoma simulating mesothelioma) has also been described and may even occur in the absence of a mediastinal component.

The patient in question is alive without known recurrence two years after surgery; however, we have seen several cases of mesothelioma recur after extended intervals. Probably only long-term follow-up will ultimately determine the true nature of this tumor.

DIAGNOSIS:

ATYPICAL MESOTHELIAL PROLIFERATION (Well Differentiated Epithelial Mesothelioma versus Florid Nodular Mesothelial Hyperplasia)
REFERENCES:


CASE #9

CLINICAL HISTORY:

A 56 year old man presented in 2/92 with 2 months of cough, fatigue and dysphagia. Chest radiograph revealed a 13x10cm left anterior mediastinal mass. Biopsy via mediastinoscopy showed ectatic blood vessels in a fibrotic stroma, and the diagnosis of cavernous hemangioma was made. The patient received 2160 rads of radiation with no response. In 6/92 a more substantial biopsy was taken. At that time, the tumor filled the left chest with extension to the diaphragm.

GROSS DESCRIPTION:

Grossly the tissue appeared pink to gray with areas of necrosis.

HISTOLOGICAL FEATURES:

This neoplasm represents a malignant germ cell tumor showing a combination of epithelial and mesenchymal elements. The epithelial component is arranged in the form of cords and tubules lined by cells with markedly hyperchromatic nuclei and high mitotic activity. Some of these tubules have a primitive neuroepithelial appearance. They are separated by an abundant edematous stroma. The mesenchymal element of the neoplasm is sometimes seen encircling the tubules and is formed by oval to spindle cells which are mitotically active.

COMMENT:

Mediastinal germ cell neoplasms are interesting for a variety of reasons. One relates to their evolution, which is largely a function of their morphologic makeup. Mature teratomas are nearly always curable simply by extirpation. Seminomas are cured in the majority of the cases with radiation therapy. All the others (malignant nonseminomatous germ cell tumors) require a combination of radiation therapy and chemotherapy, the results being similar but not identical to the testicular tumors of equivalent morphology. An event of dire prognosis in mediastinal germ cell tumors is the emergence of a sarcomatous component of "somatic" type. It is our impression that this event is more common in this location than in the gonadal site. It may take the form of angiosarcoma, rhabdomyosarcoma, or other types of sarcomas. This component is not susceptible to treatment with germ-cell-type protocols, confirming the rule that tumors respond to chemotherapy depending on their phenotypical features rather than their histogenesis. Parenthetically, another type of sarcoma that we have observed with germ cell tumors is represented by the emergence of a high-grade sarcoma (sometimes with rhabdomyoblastic differentiation) in spermatocytic seminoma, a tumor which occurs exclusively in the testis and which has never been seen associated with a nonseminomatous germ cell tumor component.

The other fascinating aspect of mediastinal germ cell tumors concerns their histogenesis. Specifically, the question that has been asked ever since this entity was first described is how to explain the presence of a germ cell tumor outside sites where normal germ cells are known to reside, i.e., the male and female gonads. Several possibilities have been proposed:
1. They could represent metastases from a gonadal or germ cell tumor which has not been detected or which has undergone spontaneous regression;\(^{(6)}\)

2. They could be of somatic cell derivation but endowed with the capacity to differentiate along germ cell type features;\(^{(3,7)}\)

3. They could represent the neoplastic alteration of a structure which — although still embryonal and "primitive" — is composed of cells which have progressed beyond the germ cell stage;\(^{(2)}\)

4. They could have arisen from germ cells which were located outside the gonads.

Of these four possibilities, the currently favored one is the fourth, at least for the mediastinal location.\(^{(1,10)}\) There is little doubt that most if not all retroperitoneal germ cell tumors in adults represent lymph node metastases from undetected or regressed gonadal primaries. This does not seem to be the case for the mediastinal tumors which, almost without exception, arise from within the thymus. The main problem with this interpretation is the fact that the presence of normal germ cells in the thymus has yet to be conclusively demonstrated. This is a strong indictment indeed considering the fact that the history of pathology is replete with attribution of tumors to hypothetical rests that were either figments of the imagination or — when real — totally unrelated to the tumors for whose occurrence they were blamed. However, the opposite argument can be made, in the sense that sometimes existence of a tumor of a certain site has preceded a description of the corresponding normal cell and has actually prefigured the discovery of the latter.

If germ cells are normally present in the thymus, why has nobody conclusively identified them at those sites? The claims in the literature on this matter are few and unconvincing.\(^{(1)}\) One could argue that they may be very difficult to detect because of their inconstancy, small density, and lack of easily identifiable features in routinely stained sections. An alternative explanation can be suggested for the apparent absence of germ cells at this site, and that is the possibility of them developing into somatic cell of one type or another. Could one think of a possible candidate for this event in the thymus? The epithelial cells and lymphocytes of this organ seem out of the question, being that their branchial pouch and bone marrow derivations, respectively, are well established.\(^{(14)}\) However, this organ contains another cell type of unknown origin and function for which a thymic location seems most incongruous: the myoid cell.\(^{(4)}\) This is a cell which has the phenotypical features of a skeletal (striated) muscle cell and which is found scattered in the medullary portion of the organ. Suggested progenitors for these cells include the thymic epithelium,\(^{(9,15)}\) neural crest,\(^{(8)}\) and prechordal mesoderm,\(^{(11)}\) but none of them have been conclusively proven. Could thymic myoid cells be of germ cell origin and thus provide an indirect evidence for the existence of the latter? The observation that foci of skeletal muscle differentiation are much more common in thymic than in gonadal germ cell tumor provides a little bit of evidence in favor of this interpretation.

**DIAGNOSIS:**

**MALIGNANT TERATOMA**
REFERENCES:


CASE #10

CLINICAL HISTORY:

An 18 year old male, previously healthy, presented in 8/91 with fevers, night sweats, chest pain, and dyspnea on exertion. A left anterior mediastinal mass was detected on CT scan. The HCG level was 479 and the AFP level was 6900. A fine needle aspirate was performed, and malignant cells consistent with germ cell tumor were found. The patient received six cycles of VIP chemotherapy which was completed on 12/13/91. The HCG and AFP levels returned to normal, but there was no radiographic change in the appearance of the tumor. On 1/20/92, a transverse sternotomy and bilateral thoracotomies were performed, with resection of the tumor.

GROSS DESCRIPTION:

The 320 gm tumor measured 10x9x6.3 cm and was circumscribed, lobulated, and surrounded by a thin capsule. Cut sections revealed numerous small cystic spaces within a tan, hemorrhagic tumor with focal myxoid areas and calcifications. The cysts contained thick mucinous material.

HISTOLOGICAL FEATURES:

Microscopically, the tumor shows teratomatous elements with a large component of endodermal structures, including well-formed large bowel mucosa, and mesoderm with innumerable lobules of cartilage and bone. No other germ cell tumor elements are recognized. On closer examination, the mesenchymal tissue show widespread abnormalities including hypercellularity, nuclear pleomorphism, and abundant mitotic activity. The nuclear pleomorphism is quite striking, and involves both nonspecific fibrous tissues, cartilage, smooth muscle, and focally exhibits skeletal muscle differentiation. However, there is no large nodular proliferation of the pleomorphic spindle cells. Infiltration is not seen either within the stroma of the teratoma or into the adjacent tissues. Focal atypia is also noted in the glandular component of the teratoma.

COMMENT:

The fundamental nature of this neoplasm is obviously that of a germ cell tumor, in this case primary within the anterior mediastinum. This is second to the gonads as the most common site for germ cell tumors to develop, and the large majority of affected patients are young adult males. Teratomas are the most common germ cell tumors to present in the mediastinum, although all germ cells tumor types (other than spermatocytic seminoma) have been described in that location. Obviously, the possibility that these lesions may represent metastases from an occult gonadal primary should be excluded clinically. The tumors are thought to originate from primordial germ cells which are misplaced during migration in embryogenesis.

This case is of interest for two reasons. As evidenced by the preoperative elevation of HCG and AFP, this neoplasm most likely arose as a mixed germ cell tumor, with elements of embryonal carcinoma and/or yolk sac tumor being irradiated by preoperative chemotherapy. The mature teratomatous components, being less sensitive to chemotherapy, remained. The perhaps more interesting question is that of the significance of the widespread nuclear pleomorphism. It is well accepted that chemotherapy itself may induce such changes both within the stromal and epithelial elements of teratomas. On the other hand, it is equally well-documented that somatic neoplasms can arise in teratomas, with sarcomas including rhabdomyosarcoma and angiosarcoma being particularly common in the mediastinum. These sarcomas may arise de novo or may follow treatment of the primary germ cell tumor with chemotherapy. Interestingly, the somatic neoplasms exhibit the same genetic abnormality (isochromosome 12p) that is commonly seen in germ cell tumors. It is of considerable importance to distinguish chemotherapy-related atypia from
somatic-type sarcoma. The presence of widespread nuclear changes without alterations in the architecture (i.e., chemotherapy effect) has been associated with a slightly higher recurrence rate (not statistically significant),(3) the recurrences consisting of germ cell elements. On the other hand, the occurrence of an invasive sarcomatous element is associated with a markedly worse prognosis,(3,5) with dissemination of the sarcomatous elements and resistance to germ cell chemotherapy. Treatment for those patients should therefore contain chemotherapy which is effective in sarcomas, in addition to germ cell therapy. It is also important to distinguish this phenomenon from immature teratoma, where the immature elements (usually of neural derivation) resemble the normal immature tissues encountered during embryogenesis. Residual immature elements after chemotherapy also impart a worse prognosis, but not as dismal as that of sarcomatous transformation. In the seminar case, the lack of an invasive growth pattern in the pleomorphic mesenchymal elements and the presence of similar degrees of atypia in stromal cells of many different types (as well as some epithelial elements) suggests that the changes are chemotherapy related. We have seen similar changes in many case of mediastinal teratomas as well as retroperitoneal metastases of germ cell tumors following chemotherapy, and despite the extreme degrees of atypia, no recurrences of sarcomatous elements have been seen, and these patients do not receive sarcoma-type chemotherapy.

DIAGNOSIS:

CYSTIC TERATOMA WITH CHEMOTHERAPY EFFECT

REFERENCES:

Tumor and Tumor-Like Conditions of the Mediastinum

ASCP Spring Seminar

<table>
<thead>
<tr>
<th>Case</th>
<th>SP#</th>
<th>Diagnosis</th>
<th>Presentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S93-08264</td>
<td>Invasive thymoma (rosettes)</td>
<td>JR</td>
</tr>
<tr>
<td>2</td>
<td>S92-18822</td>
<td>Malignant thymoma (type 1.5)</td>
<td>JR</td>
</tr>
<tr>
<td>3</td>
<td>S91-25688</td>
<td>Mucoepidermoid carcinoma</td>
<td>DK</td>
</tr>
<tr>
<td>4</td>
<td>S92-22874</td>
<td>Carcinoid</td>
<td>DK</td>
</tr>
<tr>
<td>5</td>
<td>S93-15496</td>
<td>Solitary fibrous tumor</td>
<td>JR</td>
</tr>
<tr>
<td>6</td>
<td>S92-17850</td>
<td>Thymoliposarcoma</td>
<td>DK</td>
</tr>
<tr>
<td>7</td>
<td>S92-21070</td>
<td>Reticulum cell sarcoma</td>
<td>JR</td>
</tr>
<tr>
<td>8</td>
<td>S92-06902</td>
<td>Mesothelial proliferation</td>
<td>DK</td>
</tr>
<tr>
<td>9</td>
<td>S92-14367</td>
<td>Germ cell tumor with sarcoma</td>
<td>JR</td>
</tr>
<tr>
<td>10</td>
<td>S92-01566</td>
<td>Teratoma with chemotherapy effect</td>
<td>DK</td>
</tr>
</tbody>
</table>
November 29, 1990

Juan Rosai, M.D.
Department of Pathology
Yale University School of Medicine
310 Cedar Street
New Haven, Connecticut 06510-8070

Dear Juan:

On behalf of the Anatomic Council of the ASCP, I thank you for agreeing to be the Chief Prelector for the 1994 Spring Slide Seminar on "Mediastinum." It is my understanding that you are required to have a co-prelector whose name should be submitted to me so that it can be approved by the Council no later than November, 1991.

You will be receiving specific information regarding the seminar from Dr. George F. Stevenson who is the Senior Vice President for Educational Activities Planning.

Again, let me express our appreciation for your taking on this program.

Best personal regards,

Robert E. Fechner, M.D.
Chairman, Anatomic Council

REF/njk

cc: George F. Stevenson, M.D.
    Sara J. Hollingsworth, MT(ASCP)
January 3, 1991

Robert E. Fechner, M.D.
Chairman, Anatomic Council
University of Virginia
Health Sciences Center
Surgical Pathology
Box 214
Charlottesville, VA 22908

Dear Bob:

Thanks for your letter of November 29 and your invitation for me to be the Chief Prelector for the 1994 Spring Slide Seminar on "Mediastinum". This is an invitation that I am very glad and honored to accept. I will be sending you the name of the co-prelector some time before November 1991. I will be waiting to receive more specific instructions regarding the seminar from Dr. Stevenson.

Thank you again for having chosen me for this important task.

Best personal regards,

Juan Rosai, M.D.
Professor of Pathology
Director of Anatomic Pathology

JR:ml
January 18, 1991

Juan Rosai, MD  
Department of Pathology  
Yale University School of Medicine  
310 Cedar Street  
New Haven, CT 06510-8070

Dear Dr. Rosai:

I was delighted to learn from Dr. Robert Fechner, Chairman of the CCE Council on Anatomic Pathology, that you have agreed to serve as prelector of the ASCP 1994 Spring AP Slide Seminar on Mediastinum.

Enclosed is the first fact sheet on this seminar. It will be updated as necessary as we proceed, with deletion of completed items and addition of new material, as appropriate. Please let us know if there are any problems.

I am sure that the officers of the Society would wish to join me in thanking you for accepting this assignment, now one of the most important to ASCP.

Sincerely,

George F. Stevenson, MD

Enclosure

cc: K. Ireland, MD, CCE Commissioner  
R. Fechner, MD, Chairman, Council on Anatomic Pathology  
S. Moran, Project Manager
December 26, 1991

Robert E. Fechner, M.D.
Director, Surgical Pathology
University of Virginia Medical School
Health Sciences Center, Box 214
Charlottesville, VA 22908

Dear Bob:

In checking the section of "Things to Do" in my 1991 calendar, I realized that one of them was to give you the name of the co-prelector for the 1994 Spring slide seminar on mediastinal tumors.

I propose for that individual to be Dr. David Klimstra. David has accepted a junior staff position at Memorial Sloan-Kettering Cancer Center, and is developing an expertise in the field of pulmonary and mediastinal pathology. He is an excellent speaker and an extremely promising academic pathologist. I have already approached him regarding this matter, and he has tentatively agreed to participate, pending your approval.

Best personal regards,

Juan Rosai, M.D.
Chairman, Department of Pathology

/jki
January 15, 1992

Juan Rosai, M.D.
Chairman, Department of Pathology
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021

Dear Juan:

Dr. David Klimstra will be fine for your co-prelector for the 1994 Spring Slide Seminar on mediastinal tumors. Although I do not know him, your recommendation is more than enough. Further communications regarding the details of the seminar will be coming from ASCP headquarters in Chicago. If there is anything I can do, please let me know.

Best personal regards,

Robert E. Fechner, M.D.

REF/njk

cc: George F. Stevenson, M.D.
   Sondra Moran MT(ASCP)