1350

California Tumor
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110TH SEMI-ANNUAL CANCER SEMINAR

INTRATHORACIC NEOPLASMS AND TUMOR-LIKE CONDITIONS

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110TH CTTR SEMI-ANNUAL CANCER SEMINAR:
INTRATHORACIC NEOPLASMS AND TUMOR-LIKE CONDITIONS

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Case #1

Clinical History - Acc. # 25133

A 41-year-old male truck driver presented with cough and left chest discomfort described as a "pulling sensation". He had no other complaints and specifically denied shortness of breath, wheezing, fever, chills, sweats or weight loss. He smoked 4-6 cigars a day but did not inhale. His chest was not tender, his lungs were clear to auscultation, and he had no digital clubbing. Chest radiograph demonstrated a left hilar mass. bronchoscopy revealed a partially occluded left upper lobe bronchus. Biopsies and cultures were negative, and he underwent thoracotomy. At surgery he had a poorly demarcated hilar mass which encircled the left pulmonary artery and was fixed to the left main bronchus necessitating pneumonectomy for complete removal. (Contributed by Christopher A. Gratton, M.D., Waterloo, IA)

Diagnosis: *Sclerosing Mediastinitis*

Discussion:

Sclerosing mediastinitis, also termed fibrosing mediastinitis and mediastinal fibrosis, is an inflammatory condition characterized by abnormal proliferation of collagen in response to granulomatous infection in mediastinal lymph nodes. Most cases appear to represent an unusual complication of Histoplasma infection. It has been reported slightly more often in men than women and typically affects young or middle-aged adults. Cough, dyspnea and hemoptysis are common presenting complaints. Partial or complete obstruction of mediastinal structures (e.g. superior vena cava, esophagus, tracheobronchial tree, pulmonary arteries and veins) may cause various other signs and symptoms. Imaging studies usually show a mediastinal mass, which may involve either the right or the left hilum, or the subcarinal region (see Table 1-1). The anterior mediastinum is most commonly affected, although occasional examples of predominantly posterior disease have been described. Affected patients may occasionally have associated sclerosing lesions in other anatomic sites, such as pulmonary hyalinizing granuloma, retroperitoneal fibrosis, orbital pseudotumor, and so-called tumefactive fibro-inflammatory lesions of the head and neck. The prognosis of sclerosing mediastinitis is variable and correlates directly with the location and extent of mediastinal fibrosis (see Table 1-2). A review of patients with clinical evidence of pulmonary vascular or tracheobronchial compromise found that 21 of 71 (30%) had died of their disease. Antimicrobials, steroids, and surgery have had little to offer in most cases.

Table 1-1: Radiographic Findings in 33 Patients with Sclerosing Mediastinitis
Sherrick et al. *Chest* 1994; 106:484-9

• Localized mediastinal mass	82%
• Diffuse soft tissue thickening	18%
• Narrowing/obstruction of	
— Superior vena cava	39%
— Tracheobronchial tree	36%
— Pulmonary artery	18%
— Esophagus (mid)	9%

Table 1-2: Complications of Sclerosing Mediastinitis

- SVC obstruction
  - SVC syndrome
- Tracheobronchial obstruction
  - Collapse, atelectasis
  - Post-obstructive pneumonia
- Pulmonary vein/artery obstruction
  - Secondary "venous infarcts"
  - Pulmonary hypertension
- SVC obstruction
  - SVC syndrome

The main pathologic finding in sclerosing mediastinitis is dense collagen fibrosis associated with a patchy infiltrate of lymphocytes and plasma cells. The collagen consists of haphazardly arranged thick hyalinized bundles, which raggedly permeate mediastinal soft tissues as well as contiguous structures. Calcification and metaplastic bone formation may occur within the fibrotic areas. Flieder and colleagues have suggested that the common sclerotic appearance represents the late stage in a process that begins as a more cellular proliferation of fibroblasts and myofibroblasts. The fibrosis usually surrounds necrotizing granulomas, which may contain Histoplasma, although the organisms may be extremely difficult to demonstrate. Acid-fast bacilli and Aspergillus are responsible for rare examples of this condition. The lung parenchyma may show a number of secondary changes related to occlusion of hilar structures. Indeed the secondary changes may be misconstrued as evidence of primary parenchymal lung disease, and may offer the first clue to the diagnosis in some patients. Peculiar subpleural and paraseptal infarcts are seen in some patients and result from pulmonary venous obstruction. Other evidence of chronic venous hypertension including venous sclerosis, hemosiderin deposition and mild hypertensive arteriopathy often accompanies the infarcts. In a review of reported cases of pulmonary venous obstruction

with infarction, sclerosing mediastinitis was the most common cause and accounted for 15 (68%) of 22 cases. Bronchial occlusion may also occur resulting in an endogenous lipid (obstructive) pneumonia.

The ***differential diagnosis*** includes mainly pulmonary hyalinizing granuloma, amyloidosis, progressive massive fibrosis, and nodular sclerosing Hodgkin's disease. *Pulmonary hyalinizing granuloma* is histologically identical to sclerosing mediastinitis but differs in that the fibrotic lesions are discrete pulmonary parenchymal lesions. Interestingly, pulmonary hyalinizing granuloma and sclerosing mediastinitis coexist in some patients indicating that they may share a common pathogenesis. *Nodular amyloidosis* also occurs as discrete peripheral lung masses and lacks the coarse collagen fibers characteristic of sclerosing mediastinitis. Furthermore, the collagen fibers of sclerosing mediastinitis do not have the tinctorial and ultrastructural qualities of amyloid. *Progressive massive fibrosis* may complicate a number of pneumoconioses but usually affects distal lung parenchyma. The fibrosis seen in this condition is also associated with pigment deposition and is accompanied by other parenchymal changes typical of the underlying pneumoconiosis. *Nodular sclerosing Hodgkin's disease* and other *sclerosing lymphomas* can show a pattern of collagen deposition similar to that seen in sclerosing mediastinitis and must be distinguished by finding characteristic Hodgkin's or other malignant lymphoid cells. For this reason, a diagnosis of sclerosing mediastinitis should be made with great caution on small biopsies (*e.g.* CT-guided needle biopsies) from patients suspected of having mediastinal lymphoma.

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Case #2

Clinical History - Acc. # 29225

A 62-year-old woman with a 90-pack-year smoking history presented to an outside hospital with a 4 to 5 day history of cough, productive sputum, fever, chills and shortness of breath. A chest x-ray was reported as showing bilateral pneumonia and a right lung mass. A chest x-ray performed three days later showed an 8 cm mass posterior to the right hilum with associated emphysema. CT scan confirmed the presence of a 7.5 x 7.5 x 7.0 cm mass in the region of the right lower lobe posteriorly. The mass abutted the azygos vein and trachea with associated soft tissue thickening indicating probable tracheal invasion. Fiberoptic bronchoscopy revealed extrinsic compression of the right upper lobe bronchus without definite evidence of tracheal involvement. Transbronchial needle aspiration, bronchial brushings, and bronchial biopsy were "negative for tumor", the biopsy reported as showing "polypoid, myxoid granulation tissue with acute and chronic inflammation".

Diagnosis: *Hamartoma*

Discussion:

Pulmonary hamartomas are the most common benign tumor of the lung. Goldworthy first applied the term *hamartoma* to benign lung tumors composed of a combination of adipose tissue and cartilage in 1934. The term implied that *hamartomas* were tumor-like malformations rather than true neoplasms. Several synonyms have since been used for pulmonary hamartoma including chondromatous hamartoma, hamartochondroma, and mesenchymoma. Recent studies demonstrating recombination of chromosomal bands 6p21 and 14q24 and translocations of high-mobility group proteins (HMGI-C and HMGI-C(Y)), support the view that hamartomas are clonal mesenchymal neoplasms.

Pulmonary hamartomas are uncommon, occurring in less than 0.5% of patients in large consecutive autopsy series. Middle aged or elderly adults are most commonly affected, with a peak incidence in the sixth or seventh decade of life. Rare examples have been reported in patients as young as 9 years of age. Pulmonary hamartomas are more common in men than women by a ratio of 2-3:1. Although it has been suggested that predilection for males may reflect increased detection in patients being evaluated for other underlying lung diseases that are more common in men, men accounted for the majority of patients in a large Mayo Clinic series even after excluding patients with other lung diseases. Most patients with pulmonary hamartomas are asymptomatic; the vast majority represent incidental discoveries detected during evaluation for other diseases. Symptomatic patients usually have cough related to endobronchial or extrinsic airway involvement. Pulmonary chondroma, a highly related if not identical cartilaginous lung tumor, constitutes one component of the triad (*i.e.* pulmonary chondroma + paraganglioma + gastric stromal sarcoma) described by Carney in 1977. Pulmonary chondromas/hamartomas occur in about

75% of patients with the Carney Triad, and are multiple in just under half. Indeed it has been suggested that all patients with multiple hamartomas be evaluated for other components of this syndrome.

Pulmonary hamartomas usually occur as peripheral intraparenchymal lung nodules with no lobar predilection. Endobronchial hamartomas account for about 10 percent of cases, although the majority of small (less than 0.5 cms) peripheral hamartomas appear to originate from small airways. Pulmonary hamartomas rarely are multiple, accounting for only 6 (2.8%) of 215 patients in the experience reported by Gjevre et al. Pulmonary hamartomas are benign with little or no risk of recurrence or malignant transformation. Several large series accounting for a combined total of over 500 patients demonstrated no examples of malignant transformation and only two (0.4%) local recurrences 10 and 12 years after excision. Basile et al. described a patient who purportedly experienced sarcomatous transformation shortly after resection of a pulmonary hamartoma. The significance of this single report is uncertain. There is no consistent link between pulmonary hamartomas and other primary lung neoplasms.

Hamartomas are usually small, averaging 1.5 to 2.0 cms in greatest dimension. Grossly they are well circumscribed, firm, rubbery nodules that are easily "shelled out" from surrounding lung tissue. Cleft-like spaces lined by entrapped non-neoplastic respiratory epithelium are present at the periphery of the tumor in most cases resulting in a characteristic biphasic appearance. Mature hyaline cartilage is an almost universal component and is typically intermingled with mature fat, fibromyxoid tissue, and rare smooth muscle cells. Any of the stromal components can predominate, however, resulting in a histological spectrum of neoplasms which can occasionally cause difficulties in differential diagnosis particularly when hyaline cartilage is absent or inconspicuous.

Hamartomas comprise multipotential mesenchymal cells with varying degrees of differentiation towards fibroblasts, smooth muscle, fat, and cartilage. Spindle cells in the fibromyxoid zones are consistently immunoreactive for vimentin, and focally and variably immunoreactive for S-100 protein, desmin, actin, smooth muscle actin, and glial fibrillary acidic protein. Stains for CD34 and HMB-45 are invariably negative, a feature that may be useful in separating hamartomas from intrapulmonary solitary fibrous tumors and both clear cell ("sugar") tumors and lymphangioleiomyomatosis, respectively. Ultrastructural studies demonstrate features of myofibroblastic or smooth muscle differentiation.

The ***differential diagnosis*** includes other benign tumors such as solitary fibrous tumor and sclerosing hemangioma, and perhaps more importantly

- "benign metastasizing" (*e.g.* pleomorphic adenoma, cutaneous chondroid syringoma, dermatofibroma/cutaneous fibrous histiocytoma, uterine leiomyoma), or
- low grade malignant (*e.g.* endometrial stromal sarcoma, dermatofibrosarcoma protuberans) non-epithelial tumors.

In most cases the presence of typical hyaline cartilage in pulmonary hamartomas is helpful. So-called *mesenchymal cystic hamartoma* is an unrelated lesion unlikely to represent a distinct entity in that the originally reported patients include examples of metastatic endometrial stromal sarcoma and rhabdomyosarcoma. The possibility of metastases should

always be carefully considered before making a diagnosis of hamartoma in patients with multiple lung nodules.

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Case #3

Clinical History - Acc. # 27605

A 31-year-old Vietnamese woman presented for evaluation of a left lower lobe lung mass. She complained of a chronic cough that was worse in the winter. Her cough was productive of small amounts of mucus and occasionally was blood-tinged. She had no other respiratory or systemic symptoms. She was a non-smoker but worked in a pool hall where she was exposed to large amounts of cigarette smoke. Chest radiograph and CT scans showed a large mass in the left mid-lung field. She underwent thoracotomy and left pneumonectomy.

The resected left lung was described as showing "bulging" at the horizontal fissure. Sectioning revealed a 6.9 x 5.5 x 5.4 well circumscribed mass with a "variegated red-brown to tan-yellow cut surface which bulges above the cut surface". The tumor was within the fissure and could not be "distinctly separated from either the upper or lower lobe although it appears to be predominantly in the lower lobe." (Contributed by Thomas Heinz, M.D., Orange, CA)

Diagnosis: *Sclerosing Hemangioma*

Discussion:

So-called sclerosing hemangiomas (SH) are benign lung neoplasms thought to be derived from incompletely differentiated respiratory epithelium. They typically present as slowly enlarging asymptomatic solitary pulmonary nodules. About 5% of reported patients have had multiple lesions. SH are more common in women than men by a ratio of 4-5:1. The mean age at diagnosis is usually the fifth decade of life, although they have been reported in a wide age range including the pediatric age group. Symptomatic patients most commonly complain of hemoptysis or vague chest discomfort. Rare examples of metastases to regional lymph nodes have been reported. No follow-up information is available in these anecdotal reports to indicate the significance of locoregional spread.

Grossly, SH tend to present as well circumscribed peripheral subpleural nodules with average diameters of 2 to 3 cms (range 0.4 to 8.2 cms). Occasional tumors may involve pleural surfaces. The recently published WHO international classification of lung and pleural tumors defines sclerosing hemangioma as,

> *"A tumour of uncertain type with a distinctive constellation of histological findings, including solid, papillary, sclerotic and haemorrhagic patterns. Hyperplastic type II pneumocytes line the surface of the papillary structures. The interstitial epithelioid cells are bland and uniform with pale cytoplasm. Cholesterol clefts, chronic inflammation, xanthoma cells, hemosiderin, calcification, laminated scroll-like whorls, necrosis and mature fat may be seen."*

As emphasized in this descriptive definition, the histological hallmark of SH is a heterogeneous variegated appearance resulting from a mixture of patterns: solid, hemorrhagic, papillary, and sclerotic. Two populations of epithelial cells can be identified: 1) surface cuboidal cells with phenotypic features of pneumocytes or Clara cells; 2) pale interstitial polygonal or round cells of uncertain histogenesis. Although controversial, the bulk of the evidence suggests that polygonal round cells represent the neoplastic population. Round cells have distinctive banal cytological characteristics including centrally located round to oval nuclei, inconspicuous nucleoli, and pale eosinophilic to clear cytoplasm with distinct cytoplasmic borders. Mitotic figures are rare. The cells are typically arranged in a solid or papillary growth pattern with an associated collagenous stroma containing variable numbers of pseudovascular blood-filled spaces. Hemosiderin pigment may also accompany the blood-filled spaces. An associated inflammatory infiltrate is common and frequently includes conspicuous numbers of mast cells.

The histogenesis of sclerosing hemangioma has been a matter of considerable interest since Liebow and Hubbell first suggested in 1956 that they represented endothelial-derived neoplasms. Mesothelial origin was suggested by Katzenstein and colleagues in 1983 based on a combination of ultrastructural, histochemical, immunohistochemical, and electrophoretic studies. More recent series have convincingly demonstrated an epithelial phenotype. In a critical review of 21 cases, Colby and colleagues demonstrated consistent immunoreactivity only for epithelial membrane antigen in lesional cells with focal immunoreactivity for keratin in a minority of cases. All other markers tested were consistently negative, including S-100, smooth muscle actin and various neuroendocrine markers. This contrasted sharply with a previous report of immunoreactivity for neuroendocrine markers in a large number of sclerosing hemangiomas, a finding that remains unexplained. Two more recent studies have demonstrated immunoreactivity for thyroid transcription factor-1, a specific marker for both thyroid and lung epithelium, and epithelial membrane antigen in both surface and round/polygonal cells. Staining for keratin, surfactant apoproteins and Clara cell antigen was limited to cuboidal surface cells (see Table). In one case studied, regional lymph node metastases had histologic and phenotypic characteristics of the pale polygonal cells. The authors concluded that sclerosing hemangioma may originate from primitive undifferentiated respiratory epithelium.

Table: Immunophenotype of Sclerosing Hemangioma

	TTF-1	Keratin	EMA	Surf apo-A	Chromo'nin	Synapto'sin
Surface cells	+	+	+	+	–	–
Round/ polygonal cells	+	–	+	–	–	–

The main ***differential diagnosis*** includes other low-grade epithelial neoplasms, including pulmonary *carcinoid tumors*. Careful attention to the characteristic variegated histology should be helpful in most cases. Immunostains can be useful, particularly in small biopsies, in separating SH from carcinoid tumors in that the latter are positive for neuroendocrine markers such as chromogranin.

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Case #4

Clinical History - Acc. # 29224

A 21 year old man presented with a 7 month history of a 35 lb. weight loss, progressive fatigue, and severe anemia. He had a history of recurrent childhood pneumonias and was discovered to have a right-sided intrathoracic tumor at the age of 10. Thoracotomy with attempted resection was unsuccessful, apparently due to involvement of mediastinal structures. He did well without treatment until 7 months prior to admission when he noted the onset of symptoms. A chest radiograph showed complete opacification of the right hemithorax. Chest CT scan confirmed the presence of a large mass filling the right hemithorax with complete atelectasis of the right lung. There was no evidence of chest wall or mediastinal invasion. He was treated with three courses of combination chemotherapy followed by thoracotomy and right pneumonectomy.

Diagnosis: ***Plasma Cell Granuloma***
(Inflammatory Pseudotumor, Fibrous Histiocytoma, Inflammatory Myofibroblastic Tumor)

Follow-up: He remained asymptomatic with no evidence of recurrent disease 3.5 years after surgery.

Discussion:

Plasma cell granulomas of the lung include a spectrum of lesions ranging from benign masses referred to by a confusing array of synonyms to frankly malignant sarcomas analogous to malignant fibrous histiocytomas arising in soft tissues. Plasma cell granulomas, as described by Bahadori and Liebow, encompass lesions referred to in the recently revised WHO classification of lung tumors as inflammatory pseudotumors. The WHO definition is,

> *"A spectrum of fibroblastic or myofibroblastic proliferations with a varying infiltrate of inflammatory cells, typically plasma cells, lymphocytes, and/or foamy histiocytes. The lesions may range from a primarily myofibroblastic or fibroxanthomatous appearance to one that has a heavy infiltrate of plasma cells".*

A partial list of synonyms applied to these lesions includes fibrous histiocytoma, inflammatory myofibroblastic tumor, inflammatory pseudotumor of fibrous histiocytoma type, pseudosarcomatous inflammatory myofibroblastic tumor, inflammatory myofibrohistiocytic proliferations, and fibroxanthoma. Spencer coined the term "pulmonary plasma cell/histiocytoma complex" to emphasize the histological heterogeneity that characterizes so-called inflammatory pseudotumors. The staggering profusion of terms for

plasma cell granulomas of the lung reflects the controversy and confusion regarding the pathogenesis and histogenesis of these uncommon tumors or tumor-like masses.

Plasma cell granulomas of the lung can occur in any age group, but over half of patients are less than 40 years of age. Indeed, in most series, plasma cell granulomas are the most common primary lung tumor in the pediatric age group. About one fourth of patients reported by Cerfolio and colleagues were less than 18 years of age. There is no sex predilection. Most patients present with asymptomatic solitary pulmonary nodules. Symptomatic patients tend to have nonspecific complaints of cough, fever, chest pain, hemoptysis, and/or shortness of breath. Eighteen (78%) of 23 patients recently reported from the Mayo Clinic were symptomatic, including cough in 12, but this almost certainly reflects selection bias. Various laboratory abnormalities have been described including microcytic hypochromic anemia, thrombocytosis, polyclonal hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate. One patient who presented with hypercalcemia was proven to have a calcitriol-producing tumor. Chest radiographs typically show a well circumscribed mass that ranging in size from 0.8 cm to 36 cms! Most measure 1 to 6 cms in size. Endobronchial involvement can be demonstrated in 10 to 15% of cases. The prognosis for plasma cell granulomas of the lung is excellent and most patients are cured with complete surgical resection. Recurrence can occur, however, and can result in the patient's death if surgically unresectable. Rare patients have been described with synchronous or metachronous involvement of extrapulmonary sites. It is uncertain whether these should be considered multifocal lesions or metastases, although most authors favor the former interpretation.

The long list of competing terms for these lesions attests to the histological diversity that characterizes individual cases and plasma cell granulomas as a group. The most consistent features are a background proliferation of spindle cells associated with a variably dense polymorphic infiltrate of mononuclear inflammatory cells. The spindle cells tend to be arranged in short fascicles with a focal storiform architecture. Immunohistochemical and ultrastructural studies show features of fibroblasts and myofibroblasts in various proportions. The inflammatory infiltrate comprises a mixed population of lymphocytes, plasma cells, histiocytes, and occasional eosinophils. Any individual cell type can predominate, although plasma cells and histiocytes tend to be the most conspicuous. Histiocytes may include multinucleated forms and frequently contain finely vacuolated cytoplasmic lipid droplets. Plasma cells may contain cytoplasmic Russell bodies and demonstrate a polyclonal pattern of light chain expression. A nonspecific pattern of organizing pneumonia is frequently seen at the periphery of fibrous histiocytomas. Small vessel invasion can be demonstrated in some cases and is of uncertain significance.

Evidence is accumulating that plasma cell granulomas are benign or low grade neoplasms rather than non-neoplastic inflammatory lesions. Thus the designation *inflammatory pseudotumor* has little advantage over the equally ill suited plasma cell granuloma. Pulmonary plasma cell granulomas are indistinguishable from inflammatory myofibroblastic tumors described in extrathoracic sites, and overlap with the broad family of fibrous histiocytomas. Investigations using a variety of techniques have identified cytogenetic abnormalities indicating that at least a subset of plasma cell granulomas are almost certainly neoplastic. These observations are also consistent with the rare examples of

aggressive behavior in patients with inoperable or incompletely excised tumors. Recent evidence has also identified herpesvirus-8 DNA sequences in inflammatory myofibroblastic tumors, and suggests that HHV-8 may play a role in the pathogenesis of some examples.

The ***differential diagnosis*** of plasma cell granuloma is lengthy and includes *nonspecific inflammatory reactions* secondary to various other conditions (*e.g.* proximal large airway obstruction, infection), *cryptogenic organizing pneumonia* (idiopathic bronchiolitis obliterans organizing pneumonia), *pseudolymphomas*, *low grade B-cell lymphomas*, *inflammatory sarcomatoid carcinomas*, so-called *inflammatory fibrosarcoma*, and *malignant fibrous histiocytomas*. Careful attention to the bland cytological features of plasma cell granulomas as well as application of appropriate panels of immunostains to difficult cases should resolve most of these diagnostic dilemmas.

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Case #5

Clinical History Acc. # 29220

A 44-year-old woman presented with a 6 to 9 month history of sharp, pleuritic pain involving her anterior left upper chest. Evaluation included a chest x-ray and CT scan demonstrating mild, diffuse pleural thickening in the left hemithorax with a small associated pleural effusion and loss of lung volume. The findings were, "worrisome for mesothelioma". Multiple liver nodules were also identified with radiographic characteristics of hemangiomas. An incisional biopsy of her pleura was diagnosed as tubulopapillary mesothelioma. Three weeks later she underwent extrapleural pneumonectomy.

Diagnosis: *Epithelioid Hemangioendothelioma*

Follow-up: After a long postoperative recovery period complicated by left hemothorax necessitating a second thoracotomy, she underwent adjuvant chemotherapy and radiation therapy. Approximately one year after pneumonectomy she developed metastatic disease involving the contralateral hemithorax and lung, paraspinal soft tissues, liver, and biceps muscles bilaterally.

Discussion:

Intravascular bronchioloalveolar tumor (IV-BAT) was first described as a discrete entity by Dail and Liebow in 1976, and they suggested that these unusual tumors originated from endothelial cells. Cases had been previously reported under a number of headings, and had been considered by some to represent migration of decidualized endometrial stroma to pulmonary parenchyma (so-called "pulmonary deciduosis"). More recently, IV-BAT has been recognized as a variant of epithelioid hemangioendothelioma (EH) and is thought to be analogous to their soft tissue counterparts. The 1999 WHO classification scheme includes EH with other intrathoracic soft tissue tumors and defines them as,

> *"A vascular tumour composed of short cords and nests of epithelioid endothelial cells embedded in a myxohyaline matrix. The tumours are distinctive for their epithelioid character, sharply defined cytoplasmic vacuoles, intraalveolar and intravascular growth and central hyaline necrosis."*

Pulmonary EH has a marked predilection for women (4 F:1 M) with a mean age at presentation of 39 years. Most patients present with mild respiratory complaints, including cough and shortness of breath. Chest radiographs typically show multiple bilateral nodules which are usually small (< 1 cm). Calcification is uncommon, as is hilar adenopathy. Mean survival in pulmonary EH is 4.6 years, although some patients may survive for prolonged periods of time with stable lung disease. The presence of respiratory symptoms at presentation and extensive intravascular, endobronchial, and pleural involvement imply a

worse prognosis. Interestingly, hilar adenopathy in the absence of metastases is also a poor risk factor.

Classical pulmonary EH has a distinctive histological appearance. Examination at low magnification reveals rounded subpleural or parenchymal nodules with pale infarct-like centers and a peripheral rim of polypoid tumor plugs. The tumor plugs penetrate pores of Kohn, filling air spaces in a fashion that resembles organizing pneumonia. Endobronchial and intravascular invasion is usually striking. The tumor plugs comprise a prominent myxoid matrix containing cords, tubules, and individual epithelioid cells with rounded to oval nuclei, inconspicuous basophilic nucleoli, and waxy eosinophilic cytoplasm. Occasional cells contain cytoplasmic vacuoles that displace the nucleus. Intranuclear cytoplasmic invaginations are also frequent. Immunostains can be useful in difficult cases and show immunoreactivity for factor VIII protein, UEA1 or CD31 in the majority of cases.

Variants of pulmonary EH include solitary nodules, endobronchial tumors and diffuse pleural involvement mimicking malignant mesothelioma. Primary mediastinal disease presenting as an isolated mediastinal mass has also been described. Lin and colleagues reported seven patients with EH involving serosal surfaces resembling the patient under discussion, and compared them to seven patients with angiosarcoma arising from serous membranes. The mean age of EH patients was 47 years and most were men. One case was metastatic from the right iliac bone and involved both pleura and pericardium. The remaining cases involved pleura and omentum. Patients presented with mesothelial thickening and effusions indistinguishable from classical diffuse mesothelioma. All reported patients have either had tumor recurrence or have died of their disease soon after diagnosis.

Pleural EH is often difficult to separate from either reactive fibrous pleuritis or malignant mesothelioma. Immunostains can be helpful in that the neoplastic cells of EH are usually cytokeratin negative, but positive for vimentin, CD31, CD34, and Factor VIII. Rare cases may demonstrate focal immunoreactivity for keratin, which emphasizes the need to use a panel of antibodies. Electron microscopic examination of some reported cases have demonstrated abundant intermediate filaments, micropinocytosis, occasional abortive lumens, interrupted basal lamina around cell cords and Weibel-Palade bodies.

As many as 25 percent of EH's may contain areas with significant atypia, mitotic activity greater than 1 per 10 hpf and necrosis, emphasizing the fact that in occasional cases the distinction from angiosarcoma is somewhat arbitrary and probably not clinically significant. Angiosarcoma involving serosal surfaces, like EH, occurs more commonly in men but tends to present in a somewhat older age group with a mean age of diagnosis in the sixth decade of life. Clinical findings at the time of diagnosis depend on tumor location, but often include recurrent and sometimes hemorrhagic effusions, and serosal surface thickening with or without mass lesions. Microscopically, most cases show a "biphasic" growth pattern characterized by the presence of nests or clusters of epithelioid tumor cells with a variable spindle cell component. In some instances, the spindle cell component may be neoplastic, but in the majority the spindle cell component represents reactive submesothelial fibrocytes and mesothelial cells. In most cases features considered characteristic of angiosarcoma can be identified, including the presence of microcystic spaces lined by papillary tumor

projections and endothelial lined, blood filled spaces with tumor cell tufts. The epithelioid cells generally have round to oval nuclei, a vesicular chromatin pattern, and prominent nucleolus. Nuclear pleomorphism is generally present while sharply delineated intracytoplasmic vacuoles are uncommon, two features that can be helpful in making the distinction from EH. Necrosis and mitotic activity are usually readily identifiable.

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Case #6

Clinical history - Acc. # 27825

An asymptomatic 55-year-old woman was discovered to have a lung mass during routine medical evaluation. She was a never smoker. A chest radiograph showed a mass that appeared to be at the distal portion of the aortic arch, suggesting the possibility of an aneurysm. CT scan demonstrated a vascular mass separate from the aorta. Preoperative evaluation included normal pulmonary function studies and no evidence of metastatic disease. At thoracotomy the mass was confined to the left lung. Wedge excision revealed a 3 x 2 cms gray-white tumor situated immediately beneath the pleura. Grossly involved lymph nodes were submitted separately. (Contributed by Nelson J. Quigley, M.D., Anaheim, CA)

Diagnosis: *Atypical Carcinoid Tumor*

Discussion:

Lung tumors with neuroendocrine differentiation represent a heterogeneous group of neoplasms which share certain morphologic and biochemical characteristics: 1) the presence of submicroscopic cytoplasmic dense core (neuroendocrine) granules, and 2) the capacity to synthesize neuropeptides. Neuroendocrine lung tumors comprise a spectrum of neoplasms ranging from relatively low-grade carcinoid tumors to highly malignant small cell carcinomas. Although historically all neuroendocrine tumors were thought to be derived from neural crest cells, many are now considered endodermally derived neoplasms which show neuroendocrine differentiation. This group of tumors has been the subject of considerable controversy resulting in the proposal of multiple competing and confusing classification schemes, several of which are summarized in Table 6-1.

TABLE 6-1: CLASSIFICATION OF NEUROENDOCRINE LUNG TUMORS

Revised 1999 WHO	Warren & Gould	Paladugu	Travis *et al.*	Miscellaneous
carcinoid tumor	bronchopulmonary carcinoid tumor	Kulchitsky cell ca, gr I	typical carcinoid tumor	
atypical carcinoid tumor	well differentiated neuroendocrine carcinoma	Kulchitsky cell ca, gr II	atypical carcinoid tumor	peripheral small cell ca resembling carcinoid tumor (Mark & Ramirez) peripheral small cell undifferentiated carcinoma (Gephardt et al.)
small cell ca	small cell neuroendocrine carcinoma	Kulchitsky cell ca, gr III	small cell carcinoma	
large cell neuroendocrine carcinoma	intermediate cell neuroendocrine carcinoma	--	**large cell neuroendocrine carcinoma**	atypical endocrine tumor (Neal et al., McDowell et al.) large cell neuroendocrine tumor (Hammond and Sause) large cell carcinoma with neuroendocrine differentiation (Wick et al.)

The 1981 WHO classification provided for only two types of neuroendocrine tumors: *carcinoid tumors* and *small cell carcinomas*. *Atypical carcinoid tumors* and *large cell neuroendocrine carcinomas* are widely recognized as additional categories of neuroendocrine tumors and have been included in the revised 1999 WHO classification scheme (Table 6-2). Traditional links between these tumor types have hinged on common histologic and immunohistochemical features across an admittedly broad range. Recent data using a variety of techniques highlight a combination of molecular and cytogenetic similarities and differences for which clinical significance remains to be elucidated.

TABLE 6-2: REVISED 1999 WHO HISTOLOGIC CLASSIFICATION OF LUNG CARCINOMA

1. **squamous cell carcinoma**
   variants:
   a. papillary
   b. clear cell
   c. small cell
   d. basaloid

→ 2. ***small cell carcinoma*** *(A malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The cells are round, oval, fusiform or spindle-shaped and nuclear molding is prominent. The mitotic count is high.)*
   variant:
   a. combined small cell carcinoma

3. **adenocarcinoma**
   a. acinar
   b. papillary
   c. bronchioloalveolar carcinoma
      non-mucinous (Clara cell/type II pneumocyte type)
      mucinous (goblet cell type)
      mixed mucinous and non-mucinous or indeterminate
   d. solid adenocarcinoma with mucin formation
   e. mixed
   f. variants:
      well-differentiated fetal adenocarcinoma
      mucinous ("colloid")
      mucinous cystadenocarcinoma
      signet ring
      clear cell

4. **large cell carcinoma** (An undifferentiated malignant epithelial tumor that lacks the cytologic features of small cell carcinoma and glandular or squamous differentiation. The cells often have large nuclei, prominent nucleoli and a moderate amount of cytoplasm.)
   variants:
→ ***a. large cell neuroendocrine carcinoma***
      combined large cell neuroendocrine carcinoma
   b. basaloid carcinoma
   c. lymphoepithelioma-like carcinoma
   d. clear cell carcinoma
   e. large cell carcinoma with rhabdoid phenotype

5. **adenosquamous carcinoma**

6. **carcinomas with pleomorphic, sarcomatoid or sarcomatous elements**
   a. carcinomas with spindle and/or giant cells
      pleomorphic carcinoma
      spindle cell carcinoma
      giant cell carcinoma
   b. carcinosarcoma
   c. blastoma (pulmonary blastoma)

→ 7. ***carcinoid tumor*** *(A tumor that is characterized by growth patterns such as organoid, trabecular, insular, palisading, ribbon, or rosette-like arrangements which suggest neuroendocrine differentiation. The tumor cells have uniform cytologic features with moderate eosinophilic, finely granular cytoplasm, and nuclei with a finely granular chromatin pattern. Nucleoli may be present.)*
   a. ***typical carcinoid*** *(A carcinoid tumor with less than 2 mits/2 mm^3 [10 hpf] and lacking necrosis. Some of these tumors may have cytologic atypia, increased cellularity and lymphatic invasion.)*
   b. ***atypical carcinoid*** *(A carcinoid tumor with 2 or more and less than 10 mits/2 mm^3 [10 hpf] and/or with foci of necrosis.)*

8. **carcinomas of salivary gland type**
   a. mucoepidermoid carcinoma
   b. adenoid cystic carcinoma
   c. others

9. **Unclassified carcinoma**

Carcinoid tumors

Carcinoid tumors are low-grade neuroendocrine tumors. Around 10% of patients will have regional lymph node metastases at presentation, and the 10 year survival rate is 90% or greater. Microscopically they are composed of cytologically bland cells containing regular round to oval nuclei with finely dispersed ("salt and pepper") chromatin and inconspicuous nucleoli. The cells are usually polygonal in shape and are arranged in distinct organoid, trabecular, or insular growth patterns with a delicate vascular stroma. Mitotic figures are scarce (< 2 mits/2mm^3 [10 hpf]) and necrosis is not seen. Neither cytologic atypia nor lymphatic invasion warrant a diagnosis of atypical carcinoid tumor. Indeed nuclear pleomorphism can be marked in some examples of otherwise typical carcinoid tumors, and can pose a particular problem for frozen section diagnosis. Peripherally located tumors differ in that they are often composed of closely packed spindle shaped cells. Despite this histopathologic peculiarity, peripheral carcinoid tumors have the same generally good prognosis as their centrally located counterparts.

A range of histologic variations have been described in otherwise typical carcinoid tumors (see Table 6-3). These histologic variants are useful in terms of remembering the range of histologies that occur in carcinoid tumors but are of little clinical or prognostic significance.

TABLE 6-3: HISTOLOGIC VARIANTS OF TYPICAL CARCINOID TUMOR

Stromal changes

- amyloid
- ossification/calcification
- granulomatous inflammation

Epithelial changes

- oncocytic/oxyphilic change
- signet rings/mucin
- melanin pigment

Atypical carcinoid tumors

Atypical carcinoid tumors are intermediate grade neuroendocrine tumors. This category comprises "well differentiated neuroendocrine carcinomas" in the terminology proposed by Gould and Memoli. Atypical carcinoid tumors differ from typical carcinoid tumors in that 40 to 50% of patients will have regional lymph node metastases at presentation and 10 to 20% will have distant metastases to brain, bone, liver, or adrenal glands. Twenty five to 50% of patients will die of their tumor after mean survivals ranging from 10 months to 3 years. Higher tumor stage, tumor size $\geq$3.5 cms, higher mitotic rates, and female gender are associated with a poorer prognosis.

Recently proposed criteria for diagnosis of atypical carcinoid tumors include, 1) areas of otherwise typical carcinoid, 2) necrosis and/or 2-10 mitoses/2 mm^3 [10 HPF] of

viable tumor. Cytologic atypia is also characteristic and includes an increased nucleus:cytoplasm ratio, nuclear pleomorphism, and conspicuous nucleoli. Cytologic atypia alone is not sufficient for a diagnosis of atypical carcinoid tumor, however, and should be accompanied by the above-named features. Recent studies have shown an inconstant correlation between "atypical" histology in carcinoid tumors and DNA aneuploidy. Although aneuploidy seems to be more common in atypical tumors, abnormal DNA content provides no additional prognostic information.

Syndromes resulting from ectopic hormone production in bronchopulmonary carcinoid tumor

- . carcinoid syndrome
- Cushing's syndrome
- ectopic acromegaly

Carcinoid syndrome is uncommon in patients with pulmonary carcinoid tumors, occurring in 5 to 10% of patients. Affected patients nearly always have liver metastases. Because of a greater likelihood of metastases, atypical carcinoid tumors are said to cause carcinoid syndrome more frequently than typical carcinoid tumors. Cushing syndrome occurs in about 1% of patients with typical bronchopulmonary carcinoid tumors and results from tumor secretion of corticotropin. Signs and symptoms of hypercortisolism are usually the presenting complaints. Carcinoid tumors may remain radiographically occult for as long as 10 years in this subset of patients. It has been suggested that carcinoid tumors causing the Cushing syndrome are associated with a more aggressive course. Atypical carcinoid tumors account for as many as 30% of carcinoids in this category, a finding that likely explains the more aggressive course. Cushing syndrome resulting from ectopic ACTH production has also been well characterized in patients with small cell carcinoma.

Ectopic acromegaly results from sustained hypersecretion of growth hormone (GH) or growth hormone-releasing hormone (GHRH) from a non-pituitary source. Ectopic production of GHRH accounts for the vast majority of those cases associated with extracranial neoplasms. In a review of 39 examples of GHRH-secreting tumors, bronchial carcinoid tumors were the single most common tumor type accounting for 21 (53.8%) cases. Eight (38%) were associated with metastases, suggesting once again that carcinoid tumors associated with clinically manifest ectopic hormone production may be associated with a more aggressive course.

Small cell carcinoma

Small cell carcinoma is a highly malignant epithelial neoplasm composed of relatively small cells with distinctive round to oval nuclei characterized by a diffuse ("salt and pepper") chromatin pattern and inconspicuous nucleoli. The cells generally have only scant cytoplasm and are arranged in broad sheets which frequently show large areas of necrosis. Extensive crush artifact and basophilic staining of blood vessel walls (Azzopardi phenomenon) are characteristic but not pathognomonic of this tumor.

Three variants of small cell carcinoma were recognized by the 1981 WHO classification: 1) oat cell ("lymphocyte-like") carcinoma which corresponds to the classically described small cell carcinoma, 2) intermediate cell type which differs in that the cells tend to have more cytoplasm, are less regular in contour, and are often polygonal or fusiform, 3) combined small cell carcinoma in which definite small cell carcinoma is admixed with a clearly identifiable squamous cell, adenocarcinoma or large cell component. The Pathology Committee of the International Association for the Study of Lung Cancer (IASLC) proposed separating small cell carcinoma into, 1) small cell carcinoma (pure or classical type), 2) mixed small cell/large cell carcinoma, and 3) combined small cell/non-small cell (*i.e.* squamous cell or adeno-) carcinoma (see Table 6-4). Although small cell carcinoma can be distinguished from non-small cell carcinomas with a great deal of consistency by light microscopy, subclassification is subject to frequent interobserver disagreement and is unreliable. Furthermore, a number of studies have shown that there are no significant clinical, therapeutic, or prognostic differences between subtypes. A possible exception is mixed small cell/large cell carcinomas, which have been assigned by various authors to either the intermediate or combined small cell categories. The 1999 WHO revised classification scheme includes only combined small cell carcinomas as a distinct variant.

TABLE 6-4: SUBCLASSIFICATION OF SMALL CELL CARCINOMA

WHO (1981)	IASLC (1988)	WHO (1999)
oat cell	small cell	small cell
intermediate cell		
	mixed small cell/large cell	
combined small cell	combined small cell	combined small cell

Immunostains can be useful in distinguishing small cell carcinoma, as well as other neuroendocrine carcinomas, from non-neuroendocrine tumors. There is no single immunostain that reliably distinguishes small cell carcinoma from non-small cell carcinomas, particularly non-small cell carcinomas with neuroendocrine differentiation (see below). Dr. Guinee and colleagues summarized their experience with immunophenotype of small cell carcinoma and contrasted endoscopic biopsies with open biopsies (see Table 6-6), demonstrating the greater sensitivity of open specimens. Staining patterns for the more common commercially available antibodies are summarized from the data of Travis *et al.* in Table 6-5. NSE is the least specific of the neuroendocrine markers, and should be used in combination with other antibodies such as chromogranin, leu 7, and synaptophysin. A recent report by Lyda and Weiss comparing non-small cell carcinomas to both small cell carcinomas and large cell neuroendocrine carcinomas (see below) demonstrates differences not only in immunoreactivity for standard (i.e. chromogranin and synaptophysin) neuroendocrine markers but also various classes of keratins.

TABLE 6-5: IMMUNOSTAINING PROFILE IN NEUROENDOCRINE LUNG TUMORS (EXPRESSED AS PER CENT OF CASES STAINING POSITIVELY)*

	NSE	CHR-A	LEU 7	SYN	KER	CEA
typical carcinoid (N=19)	95%	100%	89%	84%	56%	42%
atypical carcinoid (N=6)	83%	100%	100%	80%	40%	20%
small cell ca (N=4)	100%	50%	50%	100%	100%	100%
large cell NE ca (N=5)	100%	80%	40%	40%	100%	100%

*data summarized from Travis et al. *Am J Surg Pathol* 1991; 15:529-53.

TABLE 6-6: IMMUNOHISTOCHEMICAL STAINING OF SMALL CELL CARCINOMA IN BRONCHIAL (BBx) AND OPEN (OLB) LUNG BIOPSIES*

	BBx	OLB
Epithelial markers		
keratin (AE1/AE3)	100%	100%
EMA	95%	100%
CEA	55%	95%
Neuroendocrine markers		
chromogranin A	47%	60%
leu-7	24%	40%
synaptophysin	19%	5%
NSE	33%	60%
$\geq$ 1 NE marker	76%	80%

*data summarized from Guinee et al. *Am J Clin Pathol* 1994; 102:406-14.

Non-small cell neuroendocrine carcinomas

The neuroendocrine lung tumors described above can usually be diagnosed on the basis of light microscopy alone. Immunohistochemical staining for neuropeptides (*i.e.* neuron specific enolase, chromogranin, synaptophysin, serotonin, bombesin) and electron microscopy can be helpful in difficult cases but are not required for diagnosis. Application of these techniques to non-small cell carcinomas will reveal neuroendocrine differentiation in two additional group of tumors -- so-called *large cell neuroendocrine carcinomas* and *non-small cell carcinomas with neuroendocrine differentiation.*

Large cell neuroendocrine carcinoma refers to a subset of high grade neuroendocrine tumors characterized by, 1) a "neuroendocrine" histological growth pattern (*i.e.* organoid, palisading, trabecular, rosette-like); 2) "large" polygonal cells with lower N:C ratio than small cell carcinoma, coarse vesicular chromatin, and conspicuous nucleoli; 3) high (> 10/10 hpf) mitotic rate; 4) necrosis; 5) immunophenotypic and/or ultrastructural evidence of neuroendocrine differentiation. Tumors of this type have been referred to by a variety of terms (*i.e.* atypical carcinoid tumors, intermediate variant of small cell carcinoma, large cell neuroendocrine tumor, and large cell carcinoma with neuroendocrine differentiation), indicating the difficulty in separating these poorly differentiated carcinomas as a distinct nosological entity. Indeed studies of interobserver variability confirm the difficulty in identifying LCNEC as a discrete tumor category. Nonetheless, large cell neuroendocrine carcinomas appear to be highly aggressive bronchogenic carcinomas with a prognosis similar to that for small cell carcinoma. Published AFIP data indicates 5- and 10-year survivals of 33 percent and 11 percent, respectively. Although there is no consensus in the literature, it has been suggested that surgically resected tumors be excised and that advanced stage lesions be treated with combination chemotherapy similar to that employed for small cell carcinoma.

Non-small cell lung carcinomas with neuroendocrine differentiation are lung carcinomas of conventional histological type (*i.e.* squamous cell carcinoma, adenocarcinoma, large cell carcinoma) that happen to have immunophenotypic or ultrastructural evidence of neuroendocrine differentiation. These unique tumors account for 10 to 40% of non-small cell lung carcinomas. The significance of neuroendocrine differentiation in non-small cell lung carcinomas is uncertain. While some investigators have observed a more aggressive course in carcinomas with neuroendocrine differentiation, others have shown either no difference in survival or improved survival when compared to similar stage tumors that lack neuroendocrine differentiation. Additional studies are needed before any firm conclusions can be drawn regarding the value of recognizing this final category of neuroendocrine lung tumors.

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Case #7

Clinical history - Acc. # 29223

A 47 year old man was referred for evaluation of a right upper lobe mass. He was a smoker until 6 years prior to admission. Three or four months prior to admission he noted the onset of a cough. A chest radiograph showed a mass in the right upper lobe. CT scan showed dense consolidation of nearly the entire right upper lobe with associated air bronchograms. Transbronchial biopsy performed elsewhere showed adenocarcinoma. Thoracotomy with lymphadenectomy and bilobectomy was performed.

Diagnosis: *Bronchioloalveolar Adenocarcinoma*

Follow-up: Approximately 7.5 months after thoracotomy a follow-up chest radiograph showed multiple nodules in the left lung that had not been present on previous examinations. Concurrent sputum cytology was positive for adenocarcinoma.

Discussion:

Liebow originally separated bronchioloalveolar carcinoma (BAC) from other adenocarcinomas on the basis of four major histologic features which were to characterize >75% of the tumor: 1) origin distal to grossly recognizable bronchi, 2) well-differentiated or low grade cytology, 3) a propensity for aerogenous and lymphatic spread, and 4) growth along intact alveolar septa (so-called lepidic growth). Because metastatic adenocarcinomas from a variety of sites (e.g. stomach, pancreas, large and small bowel, prostate, breast) can have a similar appearance, the definition also assumes that the patient has no history of adenocarcinoma elsewhere. The new WHO classification defines BAC as a form of in-situ carcinoma:

> *"An adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion."*

BAC is usually located peripherally and can be localized, multinodular, or diffuse ("pneumonic"). Historically multifocal disease has been attributed to aerogenous or lymphatic dissemination. Recent studies suggest that multifocal disease may represent synchronous evolution of multiple independent neoplastic clones (*i.e.* multiclonal disease). Several studies have indicated that if strict histologic criteria are used, the localized form of BAC (i.e. stage I) has a better prognosis than ordinary stage I adenocarcinoma. Prognosis for BAC is stage dependent, and tumors presenting with multinodular or diffuse lung involvement have a worse prognosis.

Histologically, BAC may be divided into mucinous and non-mucinous ("hobnail") types. A sclerosing variant has also been described, but recent studies suggest that this subtype may have more in common with conventional adenocarcinomas than BAC. Both

mucinous and non-mucinous types are defined by the presence of cytologically bland cuboidal or columnar cells arranged in a characteristic lepidic growth pattern along apparently preserved alveolar septa. Affected alveolar septa may be thickened by fibrous tissue or a chronic inflammatory cell infiltrate. A focal or patchy "bronchioloalveolar-like" growth pattern can be seen in otherwise conventional adenocarcinomas, and therefore the term should be restricted to those carcinomas in which other glandular growth patterns are lacking. Immunophenotypic and ultrastructural studies indicate that the neoplastic cells comprising non-mucinous BAC's are derived from Clara cells and type 2 pneumocytes. Mucinous BAC is more likely to present as a multinodular or diffuse neoplasm, and has a significantly worse prognosis than the non-mucinous form.

Several investigators have focused on the relationship between BAC and benign epithelial proliferations. An analogy to colonic adenocarcinoma has been proposed suggesting that there may be a spectrum of epithelial proliferations in the lung ranging from benign hyperplasia or adenomas to atypical adenomatous hyperplasia (AAH) to fully developed adenocarcinomas. The results remain controversial, however, and there is no clear evidence that one can reliably identify a "precursor" lesion of BAC. Nonetheless, hyperplasia of alveolar lining cells can occasionally mimic the appearance of BAC in biopsy specimens. Pneumocyte hyperplasia usually differs from BAC in that it occurs in the setting of another underlying process, such as UIP or chronic bronchiolitis.

Mucin may be a prominent feature in rare non-bronchioloalveolar lung tumors. Reported examples range from low grade tumors of uncertain malignant potential to high grade tumors with signet ring cells. Non-bronchioloalveolar adenocarcinomas with prominent mucin production account for most of the new adenocarcinoma "variants" (i.e. mucinous ["colloid"], mucinous cystadenocarcinoma, and signet ring types) included in the new WHO classification. Several authors have detailed cystic tumors analogous to mucinous cystadenomas occurring in extrapulmonary sites. All presented as peripherally situated cystic tumors. Women outnumbered men by 8 to 5, and ages ranged from 41 to 71 years (mean 58 years). All patients are alive without recurrence after 1 to 9 years of follow-up.

Mucinous cystadenocarcinomas present as circumscribed unilocular cysts containing abundant mucin. Mucin dissects into adjacent pulmonary parenchyma in a minority of cases. A single layer of columnar mucus cells lines the cyst wall with bland cytologic features. The main differential diagnosis is bronchioloalveolar carcinoma. This distinction depends on recognition of the distinctive lepidic growth pattern of bronchioloalveolar carcinoma, as opposed to the non-invasive appearance of these rare cystic tumors. Other tumors may also occasionally have abundant mucin, particularly mucoepidermoid carcinomas. Diagnosis in these cases depends on finding areas with the combined histologic features typical of mucoepidermoid carcinomas.

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Case #8

Clinical history - Acc. # 28555

A 55-year-old man, described as a heavy cigarette smoker, presented with hemoptysis. A chest radiograph demonstrated a large mass in the left lower lobe. The patient was told that he "probably had cancer" but initially declined further evaluation. He returned with recurrent hemoptysis and was hospitalized. CT scan of the chest confirmed the presence of a large left lower lobe mass and mediastinal adenopathy. CT scan of his brain showed no evidence of metastases. Percutaneous needle biopsy was non-diagnostic; bronchoscopy yielded diagnostic tissue. He underwent thoracotomy and was discovered to have a "very large tumor mass involving virtually all of the lower lobe." Lobectomy was performed. The resected lobe weighed 550 grams and was largely replaced by a 7.5 x 7.0 x 5.5 cm centrally necrotic yellowish mass. (Contributed by Philip Robinson, M.D., Boynton Beach, FL)

Diagnosis: *Large Cell (Neuroendocrine?) Carcinoma*

Discussion:

Large cell carcinoma (LCC) refers to those non-small cell carcinomas that show no differentiating features (i.e. evidence of squamous or glandular differentiation). Thus, LCC is always a diagnosis of exclusion and should not be applied to small cytology or biopsy samples.

1999 WHO CLASSIFICATION OF LARGE CELL CARCINOMA

large cell carcinoma — *An undifferentiated malignant epithelial tumor that lacks the cytologic features of small cell carcinoma and glandular or squamous differentiation. The cells often have large nuclei, prominent nucleoli and a moderate amount of cytoplasm.*

variants:

a. large cell neuroendocrine carcinoma
   combined large cell neuroendocrine carcinoma (*a large cell neuroendocrine carcinoma with components of adenocarcinoma, squamous cell carcinoma, giant cell carcinoma and/or spindle cell carcinoma)*
b. basaloid carcinoma
c. lymphoepithelioma-like carcinoma
d. clear cell carcinoma
e. large cell carcinoma with rhabdoid phenotype

As the definition implies, LCC represents a "wastebasket" category for unclassifiable and poorly differentiated carcinomas. Ultrastructural studies and/or immunohistochemistry usually demonstrate evidence of differentiation along squamous, glandular, or neuroendocrine lines in almost 90% of cases. LCC usually presents as a large peripheral mass with prominent necrosis. Clinical behavior mirrors that of other poorly differentiated or high grade non-small cell carcinomas, meaning that LCC tends to be associated with an aggressive course.

Histologically, LCC is characterized by sheets of round to polygonal cells with clear to faintly eosinophilic cytoplasm without differentiating features. The diagnosis of malignancy is straightforward, although in some cases the ***differential diagnosis*** might include non-epithelial neoplasms such as *anaplastic large cell lymphoma* and *malignant melanoma*. Immunostains can be helpful in that LCC usually demonstrate immunoreactivity for keratins and epithelial membrane antigen. Potential pitfalls include rare reports of immunoreactivity for CD45 and occasional immunoreactivity for markers typically associated with germ cell tumors (*e.g.* hCG and alpha-fetoprotein).

A number of rare variants have been described, the most important of which may be so-called large cell neuroendocrine carcinoma. Indeed, many may argue that the case under discussion has a "neuroendocrine" growth pattern, the diagnosis of LCNEC hinging on the results of immunostains for neuroendocrine markers (see Case 6 for discussion of LCNEC). Basaloid carcinomas are histologically identical to basaloid carcinomas of the upper aerodigestive tract and have been described mainly in lung carcinoma series from France where they tend to be associated with a worse prognosis than other non-small cell lung carcinomas. Lymphoepithelioma-like carcinomas are virtually indistinguishable from their more common nasopharyngeal counterpart and show the same relationship to Epstein-Barr virus infection. Clear cell change is relatively common in conventional squamous cell and adenocarcinomas and is not specific for LCC. Although giant cell carcinomas were historically considered variants of LCC, the revised WHO classification scheme reserves a special category for *carcinomas with spindle and/or giant cells* (see Case 10 for discussion).

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Case #9

Clinical History - Acc. # 29162

An 89-year-old man presented for evaluation of a persistent radiographic abnormality in the upper lobe of his left lung. Three months prior to admission he was hospitalized elsewhere for pneumonia which was treated with antibiotics. Follow-up radiographs demonstrated a smaller but persistent left upper lobe infiltrate. He is currently asymptomatic without cough, fever or chills. His past medical history includes multiple total hip and knee arthroplasties, macular degeneration, hypertension, partial penectomy for squamous cell carcinoma, and cutaneous squamous cell carcinoma. He was formerly employed as a grain elevator operator and maintenance man. CT scan showed a "diffuse wedge-shaped infiltrate in the left upper lobe anteriorly . . . looks more like an infiltrate than a mass." He underwent left upper lobectomy following bronchoscopic biopsy.

Diagnosis: *Adenocarcinoma arising in Usual Interstitial Pneumonia*

Follow-up: He died 6 weeks after surgery.

Discussion:

Usual interstitial pneumonia is the "usual" finding in patients who present with chronic interstitial pneumonia of unknown etiology, or idiopathic pulmonary fibrosis (IPF) (also referred to as cryptogenic fibrosing alveolitis). Most cases are sporadic, occurring in patients who present in the 5th or 6th decade of life complaining of slowly progressive dyspnea and nonproductive cough. Men are affected more commonly than women by a ratio of nearly 2:1. Rare familial cases of IPF have been described. Although no consistent risk factors have been identified, a history of cigarette smoking is common in affected patients. Chest radiographs show diffuse interstitial opacities associated with reduced lung volumes. High resolution CT (HRCT) scans show a characteristic pattern of peripheral (subpleural) and bibasilar reticulonodular opacities associated with architectural distortion including honeycomb change and traction bronchiectasis. IPF usually follows a relentlessly progressive course with most patients dying of respiratory failure within 5 to 10 years of diagnosis. Most patients succumb to respiratory failure. Bronchogenic carcinoma is the third leading cause of death in patients with IPF, accounting for about 10% of disease-related deaths.

Usual interstitial pneumonia has a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change. The histological changes affect peripheral subpleural parenchyma most severely. The interstitial inflammation is usually patchy and consists of an alveolar septal infiltrate of lymphocytes, plasma cells, and histiocytes associated. The fibrotic zones are composed

mainly of dense acellular collagen, although scattered foci of fibroblast proliferation may also be seen. Areas of honeycomb change are composed of cystic fibrotic air spaces which are frequently lined by bronchiolar epithelium and filled with mucin. Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change. A range of epithelial abnormalities accompany the interstitial abnormalities, including hyperplasia of alveolar lining cells and bronchiolar epithelium, metaplasia of bronchiolar epithelium, and varying degrees of reactive atypia. In occasional patients the degree of reactive atypia may raise a suspicion for adenocarcinoma.

A link between pulmonary fibrosis and carcinoma has been a matter of considerable interest and speculation since 1939 when Friedrich first described peripheral carcinomas arising in focal scarring. Subsequent investigators have described carcinoma arising in diffuse pulmonary fibrosis of various etiologies. Meyer and Liebow identified honeycomb change in lung 32 (21%) of 153 consecutive surgical resections for lung carcinoma. All were male smokers, the majority over 60 years of age, who developed peripheral carcinomas predominantly in the upper lobes. Meyer and Liebow demonstrated transition between areas of atypical epithelium and adjacent carcinoma, and concluded that carcinomas arose from atypical hyperplasia within areas of honeycomb change. Since that time most studies of carcinoma arising in patients with IPF either lack specific histological categorization of the underlying lung disease or have included patients with other associated conditions such as collagen vascular disease or asbestosis.

Carcinoma arising in UIP is more common in men than women and usually affects those with a history of cigarette smoking. The risk for developing carcinoma appears to be greater than that explained by a smoking history alone. Most present with peripheral lung lesions. About half are asymptomatic while the rest are associated with the onset of new respiratory complaints such as worsening shortness of breath, hemoptysis, fatigue, weight loss, and/or chest pain. The prognosis for patient with UIP who develop is poor but not significantly different for matched controls with either UIP or carcinoma alone, reflecting the dismal prognosis associated with all of these conditions. Somewhat surprisingly, squamous cell carcinoma is the most common histologic tumor type in patients with underlying UIP, representing 16 (67%) of 24 cases recently reviewed from the Mayo Clinic files. Adenocarcinoma may be difficult to separate from the more common reactive non-neoplastic epithelial changes. The key to recognition of carcinoma is a combination of cytologic atypia and a departure from the architecture of the underlying fibrotic disease, usually in the form of stromal invasion.

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Case #10

Clinical history - Acc. # 29226

An asymptomatic 62-year-old man with a remote history of melanoma presented for evaluation of a new left upper lobe lung lesion. He had a 40-pack-year smoking history but quit 10 years ago. His history of melanoma dated to a skin biopsy from his back 10 years prior to admission. Review of the initial skin biopsy confirmed the presence of an incompletely excised invasive melanoma with a maximum tumor thickness of at least 1.5 mm (Clark's level III); he underwent wide re-excision approximately two weeks after biopsy. Three years later he developed ipsilateral axillary adenopathy and underwent lymphadenectomy that was reported to show metastases involving six lymph nodes. He received adjuvant chemotherapy for one year following lymphadenectomy. Routine chest x-ray showed a 2.8 cm mass in the left upper lobe that was not present two years previously. Additional staging studies revealed no evidence of tumor elsewhere. He underwent thoracotomy. A wedge biopsy from his left upper lobe demonstrated a 3 cm partially necrotic mass. All sampled mediastinal lymph nodes were negative for tumor.

Diagnosis: *Pleomorphic (Sarcomatoid) Carcinoma*

Follow-up: Four months later he experienced a partial motor seizure. CT scan demonstrated a 2.8 cm solitary tumor in the right posterior superior parietal lobe. Biopsy demonstrated metastatic sarcomatoid carcinoma, for which he underwent debulking and radiation therapy. He died 9 months after thoracotomy.

Discussion:

A number of primary malignant spindle cell tumors occur in the lung including biphasic (epithelial + mesenchymal) neoplasms and monophasic sarcomas. Biphasic neoplasms, excluding malignant mesothelioma, have historically been grouped into three main categories: 1) spindle cell carcinoma, 2) carcinosarcoma, and 3) pulmonary blastoma. The revised WHO classification scheme creates a new category for "carcinomas with pleomorphic, sarcomatoid or sarcomatous elements" and maintains separation of sarcomatoid carcinomas ("carcinomas with spindle and/or giant cells") from carcinosarcoma and pulmonary blastoma. As a further refinement, however, it further subdivides sarcomatoid carcinomas into pleomorphic, spindle cell, and giant cell types. The clinical value of subdividing sarcomatoid carcinomas into these histologic categories remains dubious at best.

Sarcomatoid carcinomas of any subtype and carcinosarcomas are highly malignant neoplasms that usually present in the sixth or seventh decade of life as bulky tumors. Men are affected more commonly than women by a ratio of 3-to-1, and most are current or former cigarette smokers. A minority present as predominantly endobronchial lesions.

Nearly half of patients present with clinical and pathologic stage I disease. Despite a tendency to present with relatively low stage disease, the prognosis is poor with mean survivals of about one year.

Traditionally *spindle cell carcinoma* was considered a subtype of squamous cell carcinoma (1982 WHO classification), defined by the presence of a typical squamous cell component admixed with sarcomatoid areas composed of spindle shaped cells. Spindle cell carcinomas are not unique to neoplasms of squamous origin, however, and can have a purely adenocarcinomatous, adenosquamous or undifferentiated large cell component. Combined small cell and spindle cell carcinoma has also been described. The most recently published WHO classification scheme groups tumors with "pleomorphic", sarcomatoid and sarcomatous elements (see Table 10-1). The term pleomorphic carcinoma was created to emphasize the frequent coexistence of spindle cell and giant cell areas in poorly differentiated sarcomatoid carcinomas. Spindle cell and giant cell carcinomas stand apart in that they comprise a purely spindle cell or giant cell component, respectively.

TABLE 10-1: 1999 WHO CLASSIFICATION OF MALIGNANT EPITHELIAL TUMORS — SARCOMATOID LUNG TUMORS —

- **Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements** (*A group of poorly differentiated non-small cell carcinomas that contain a component of sarcoma or sarcoma-like elements.*)
  - **Carcinomas with spindle and/or giant cells**
    - **Pleomorphic carcinoma**
    - **Spindle cell carcinoma**
    - **Giant cell carcinoma**
  - **Carcinosarcoma**
  - **Pulmonary blastoma**

The term *carcinosarcoma* is generally reserved for those tumors in which a distinct carcinomatous component is juxtaposed with a malignant stromal component that can be classified as a specific type of soft tissue sarcoma (*e.g.* osteosarcoma, rhabdomyosarcoma). The most common combination is squamous cell carcinoma plus fibrosarcoma or malignant fibrous histiocytoma. Theoretically, immunohistochemistry and electron microscopy show evidence of epithelial differentiation in the sarcomatoid areas of sarcomatoid carcinomas, in contrast to the sarcomatous areas of carcinosarcomas which lack all evidence of an epithelial phenotype. Increasingly it has been demonstrated that there is little theoretical or clinical difference between these two categories and several authors have suggested that this distinction be abolished. Using a novel molecular technique, Thompson and colleagues analyzed clonality in six carcinosarcomas (including one from the lung) and showed clonal identity for the carcinomatous and stromal components in all cases. The authors concluded that carcinosarcomas arise from a single totipotential stem cell with divergent differentiation. Yousem and colleagues have demonstrated homologous p53 mutations in a

subset of spindle cell carcinomas and carcinosarcomas also suggesting origin from a single precursor cell. Wick and colleagues have proposed that all such tumors be grouped under the general heading of sarcomatoid carcinoma with subdivision into biphasic and monophasic types (see Table 10-2).

TABLE 10-2: CLASSIFICATION OF SARCOMATOID CARCINOMA AS PROPOSED BY WICK ET AL.

- Biphasic sarcomatoid carcinoma
  - "Homologous"
  - "Heterologous"
- Monophasic sarcomatoid carcinoma
- Special variants
  - pulmonary blastoma
  - pseudoangiosarcomatous carcinoma
  - inflammatory sarcomatoid carcinoma

Inflammatory sarcomatoid carcinomas are different from other tumors in this category in that the neoplastic cells are deceptively bland, and therefore the diagnosis of malignancy can be missed altogether. The neoplastic cells of inflammatory sarcomatoid carcinomas are predominantly spindled and are arranged in a relatively haphazard pattern with no distinct architectural features. The key to diagnosis is thorough sampling. In most cases foci can be identified in which the cells assume a more pleomorphic, epithelioid appearance thus resembling carcinoma. A paradoxical propensity to invade blood vessels is also an important clue to the diagnosis. In some cases immunohistochemistry can be extremely helpful in demonstrating reactivity for keratins in neoplastic spindle cells. Despite the deceptively innocuous appearance of this subset, inflammatory variants carry the same grim prognosis as other forms of sarcomatoid carcinomas.

The ***differential diagnosis*** of sarcomatoid carcinoma includes mainly *primary pulmonary sarcomas*. Primary pulmonary sarcomas usually present in adults as large circumscribed peripheral tumors, and are classified using the criteria applied to soft tissue sarcomas. Fibrosarcomas and leiomyosarcomas have been most frequently reported, followed by malignant fibrous histiocytoma, hemangiopericytoma, osteosarcoma, and chondrosarcoma. More recently *monophasic synovial sarcomas* are increasingly recognized as a form of primary pulmonary or pleural sarcoma. Distinguishing sarcomatoid carcinomas from primary sarcomas depends primarily on demonstrating evidence of epithelial differentiation on either routine sections or with the use of immunohistochemistry or electron microscopy. As in all of pathology the results of special studies must be carefully correlated with histologic findings. There are almost certainly monophasic sarcomatoid carcinomas in which an epithelial origin cannot be "objectively" demonstrated. Conversely focal aberrant expression of epithelial-associated intermediate filaments is a well recognized diagnostic pitfall in occasional soft tissue sarcomas. Distinguishing sarcomatoid carcinomas

from monophasic or biphasic *malignant mesotheliomas* is usually less problematic in that mesotheliomas typically form diffuse pleural rinds rather than bulky lung masses.

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Case #11

Clinical history - Acc. # 25743)

A 64-year-old retired gardener with a 90-pack-year smoking history presented for evaluation of suspected deep venous thrombosis of his left leg. Admission chest x-ray showed a "massive infiltrate" involving the right lower lobe. He was treated with oral antibiotics for presumed pneumonia and developed hemoptysis accompanied by fevers and chills. He was re-evaluated and percutaneous needle biopsy was performed yielding a diagnosis of non-small cell carcinoma. He underwent resection of right middle and lower lobes. The bilobectomy specimen demonstrated a 7 x 6 cms mass in the lower lobe described as "firm white, mucinous material with cystic areas of necrosis and degeneration." (Contributed by Josef Kollin, M.D., Long Beach, CA)

Diagnosis: *Pulmonary Blastoma*

Discussion:

Pulmonary blastoma is grouped with other "carcinomas with pleomorphic, sarcomatoid or sarcomatous elements" in the revised WHO classification (see Table 10-1), and as a specialized variant of sarcomatoid carcinoma in the terminology proposed by Wick (see Table 10-2). Traditionally pulmonary blastoma has been set apart based on distinctive histology characterized by a combination of primitive blastematous mesenchyme and a neoplastic glandular component resembling fetal lung. Spencer coined the term *pulmonary blastoma* to describe this rare biphasic lung neoplasm previously reported as *embryoma of the lung*. The WHO classification defines pulmonary blastoma as,

> *"A biphasic tumour containing a primitive epithelial component that may resemble well-differentiated fetal adenocarcinoma and a primitive mesenchymal stroma, which occasionally has foci of osteosarcoma, chondrosarcoma or rhabdomyosarcoma."*

Defined in this way, pulmonary blastoma is a distinct and separate entity from *pleuropulmonary blastoma*, a special form of intrathoracic sarcoma seen almost exclusively in infants and young children (see Case 19). The literature is confusing, however, in that the term *pulmonary blastoma* has frequently been applied to both tumors.

Pulmonary blastomas are rare, accounting for less than 1% of malignant lung tumors. Although the age distribution is difficult to sort-out given "contamination" of the literature by examples of childhood pleuropulmonary blastomas, most affected patients are adults with a mean age at diagnosis in the fourth decade of life. Men and women are affected equally. As with other forms of sarcomatoid carcinomas, most patients have a history of cigarette smoking. The majority of patients (80%) are symptomatic at the time they are discovered to have large, peripheral masses. Tumors average around 10 cms in greatest dimension (range 2 to 27 cms). About half will have associated pleural effusion. The prognosis is similar to

other conventional forms of high grade or poorly differentiated lung carcinoma; fewer than 10% of patients survive 10 years. Locoregional sites of metastases include mediastinal lymph nodes, lung, pleura, chest wall, and diaphragm; brain is the most common site for distant relapse.

Classical pulmonary blastoma is a biphasic tumor in which the epithelial component is an adenocarcinoma. The adenocarcinomatous component shows a range of growth patterns, including areas with an acinar architecture reminiscent of that seen in endometrioid carcinomas. The histologic overlap with endometrioid tumors includes the presence of morules and/or squamous differentiation in about half of cases. Neoplastic glandular cells often have clear cytoplasm due to the presence of abundant glycogen that is easily demonstrated with PAS stains. Neoplastic epithelium is immunoreactive for keratin, epithelial membrane antigen, and CEA, and frequently stains for neuroendocrine markers such as chromogranin and neuron specific enolase. Focal immunoreactivity for surfactant apoprotein and Clara cell antigen is also common. In addition, some tumors may elaborate alpha-fetoprotein and thus mimic endodermal sinus tumor. The stromal component consists of primitive appearing "blastema" comprising small, blunt, spindle cells with minimal nuclear pleomorphism. Various forms of "heterologous" differentiation are common including fibrosarcoma, rhabdomyosarcoma, leiomyosarcoma, chondrosarcoma and osteosarcoma. The blastematous component is invariably immunoreactive for vimentin and focally immunoreactive for a variety of muscle-associated antigens including desmin, actin, and myoglobin. S-100 staining is generally limited to areas with cartilaginous differentiation.

The unique combination of histologically distinctive glandular and stromal elements that defines pulmonary blastoma was initially thought homologous to the "pseudoglandular" stage of lung development at 10 to 16 weeks gestation. This prompted Spencer to conclude that pulmonary blastomas arose from pluripotent mesenchyme (*i.e. blastema*) in a manner analogous to the proposed histogenesis of nephroblastoma. Yousem and colleagues demonstrated significant overlap in a comparative immunohistochemical study of pulmonary blastomas and fetal lungs, further suggesting that classical biphasic blastomas are sarcomatoid carcinomas demonstrating many of the same characteristics as developing pulmonary blastema.

The histologic and immunohistochemical features of the epithelium in pulmonary blastoma are virtually indistinguishable from so-called *well-differentiated fetal adenocarcinoma* (also called adenocarcinoma of fetal type, well differentiated adenocarcinoma simulating fetal lung tubules, and endodermal tumor resembling fetal lung). The revised WHO scheme describes well-differentiated fetal adenocarcinoma as a variant of adenocarcinoma showing,

> *". . . a pattern resembling fetal lung tubules. The epithelial component has a distinctive appearance consisting of glandular elements composed of tubules of glycogen-rich, non-ciliated cells that resemble fetal lung tubules. Subnuclear and supranuclear glycogen vacuoles give the tumour an endometrioid appearance. Rounded morules of polygonal cells with abundant eosinophilic and finely granular cytoplasm are common."*

Many consider well-differentiated fetal adenocarcinoma a monophasic, purely epithelial variant of pulmonary blastoma. Indeed the WHO monograph goes on to say,

> *"The well-differentiated fetal adenocarcinoma pattern may be seen as the epithelial component of* pulmonary blastomas *that have a biphasic pattern. Therefore, on a small biopsy specimen, one cannot exclude the possibility of a biphasic* pulmonary blastoma *if the pattern of* well-differentiated fetal adenocarcinoma *is identified."*

Regardless of how one views the relationship between pulmonary blastoma and well-differentiated fetal adenocarcinoma, the latter tends to have a better prognosis (see Table 11-1).

TABLE 11-1: COMPARISON OF WELL-DIFFERENTIATED FETAL ADENOCARCINOMA (WDFA) AND CLASSICAL BIPHASIC PULMONARY BLASTOMA

Modified from Colby et al. Atlas of Tumor Pathology (Third Series, Fascicle 13). *Tumors of the Lower Respiratory Tract*. Armed Forces Institute of Pathology. Washington, DC 1994, p. 396

	WDFA	**Biphasic Blastoma**
CLINICAL		
% patients < 10 years of age	0	8%
History of cigarette smoking	Common	Common
Location	Lung	Lung
Average size	4.5 cms	10.1 cms
Asymptomatic	Often	Uncommon (~ 20%)
Prognosis	Good	Poor
PATHOLOGIC		
Malignant epithelium/ Malignant stroma	Present/Absent	Present/Present
Morules present	86%	43%
Neuroendocrine differentiation	Frequent	Frequent

Reference:

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Case #12

Clinical History - Acc. # 29221

A 40 year old woman with a history of respiratory papillomatosis presented for evaluation of enlarging lung nodules. She initially presented with a soft voice and hoarseness at 2 years of age and was discovered to have multiple laryngeal and tracheal papillomas. Over her first decade of life she underwent multiple excisions of upper respiratory tract papillomas. At 11 or 12 years of age she underwent resection of a right lower lobe lung nodule and at the age of 17 or 18 years underwent resection of multiple left lung nodules. She underwent resection of additional right lung nodules at the age of 21 and has had no lung surgeries since that time. She has continued to have multiple excisions of upper respiratory tract lesions. Serial chest x-rays showed a slowly enlarging right lower lobe nodule and she was referred to the Mayo Clinic for further care. She complained of mild dyspnea on exertion and a dry cough without hemoptysis. She was a former smoker, having smoked one pack of cigarettes per day for 26 years until three years prior to admission. Repeat CT scan showed multiple nodules and masses throughout the right lung, many of which appeared cavitated. The largest nodule measured 3 x 2.5 cms. She underwent repeat right thoracotomy and wedge excision of multiple right lower lobe nodules.

Diagnosis: ***Respiratory (Juvenile Laryngotracheal) Papillomatosis forming multiple nodules without invasive growth, angiolymphatic invasion or other evidence of malignant transformation***

Discussion:

Respiratory papillomatosis, also referred to as juvenile laryngeal or laryngotracheal papillomatosis, is a form of human papillomavirus (HPV)-mediated papillomatosis that typically presents in childhood. Boys and girls are affected equally. The most common presenting complaints are hoarseness, change or loss of voice, cough, respiratory distress and stridor. Nearly all patients present prior to the age of 6 years. HPV-11 and HPV-6 have been most commonly implicated and are likely perinatally acquired from mothers with genital infection. HPV DNA has been demonstrated in histologically uninvolved respiratory epithelium in patients with active disease as well as patients who are otherwise in remission. The true vocal cords are affected first followed by spread to the false cords, epiglottis, and supraglottis. The trachea and bronchi are only occasionally involved. Surgical excision or laser ablation are the mainstay of therapy for patients with symptomatic disease or significant airway limitation. Recurrences are common frequently necessitating multiple surgical procedures. Other adjuvant therapies, such as interferon, have been employed with variable results. Spontaneous regression can occur. Squamous cell carcinoma ("malignant degeneration") is uncommon but can affect either the upper or lower respiratory tracts.

Cigarette smoking and radiation therapy are risk factors associated with a greater likelihood of developing malignant disease.

Histologically respiratory papillomatosis is characterized by multiple exophytic papillary or acanthotic excrescences comprising bland non-keratinizing squamous cells with surface maturation. Mitotic figures and mild cytologic atypia, with or without associated koilocytotic change, are common and may thus mimic well differentiated carcinoma. Distinction from squamous cell carcinoma depends in part on lack of an invasive growth pattern coupled with the characteristic clinical and gross pattern of disease. In rare cases respiratory papillomas can involve tracheostomy stoma sites and/or perilaryngeal soft tissues ("invasive papillomatosis") further mimicking the appearance of carcinoma.

Lung involvement is rare, occurring in less than 1% of cases. Peripheral parenchymal disease need not be accompanied by involvement of proximal bronchi. Lung disease usually presents as multiple asymptomatic nodules that may be cystic or solid. Cystic lesions can form thick-walled cavities with associated air-fluid levels thus resembling cavitating carcinomas. Large thin walled cystic lesions also occur and can be confused with other cystic processes such as pulmonary eosinophilic granuloma (Langerhans' cell granulomatosis/histiocytosis), lymphangioleiomyomatosis or even emphysema. Histologically the lung nodules correspond to peculiar intra-alveolar tufts of papillomatous squamous epithelium distributed along alveolar septa in a manner resembling that seen in bronchioloalveolar forms of adenocarcinoma. The circumscribed clusters of proliferating squamous cells are centered on distal airways and frequently show a complex relationship with columnar respiratory epithelium that includes areas of squamous metaplasia. Some nodules are associated with perinodular airspace enlargement similar to that seen with other slowly growing peribronchiolar neoplastic or non-neoplastic conditions such as hamartomas, metastatic low grade sarcomas, and pulmonary eosinophilic granuloma. Other nodules may show central squamous-lined cavities that likely result from airway obstruction, post-obstructive pneumonia and associated necrosis. True tumor necrosis is uncommon and should raise a suspicion of malignant degeneration. Distinguishing peripheral lung involvement from squamous cell carcinoma can be difficult and is predicated on recognition of cytologic atypia as well as a destructive growth pattern with an associated desmoplastic reaction. Squamous cell carcinomas have been described in patients with respiratory papillomatosis confined to the larynx without peripheral lung involvement.

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Case #13

Clinical history - Acc. # 29163

A 33 year old previously healthy man presented with a 6 week history of hemoptysis and fever. Chest x-ray showed bilateral infiltrates and questionable nodules. HIV serology was negative. PFTs showed severe restriction with severely reduced diffusion capacity. Sputum, cultures, and bronchoscopy failed to yield a diagnosis. His condition progressed despite a trial of corticosteroids for presumed sarcoidosis, and he underwent thoracotomy with open lung biopsy. He died 2 weeks later and an autopsy was performed. (Contributed by Peter J. Benson, M.D., Robbinsdale, MN)

Diagnosis: *Metastatic Angiosarcoma*

Follow-up: Autopsy demonstrated a primary angiosarcoma involving the right cardiac atrium with extensive hemorrhagic metastases to both lungs.

Discussion:

Pulmonary hemorrhage is rarely the presenting manifestation of angiosarcoma. Patients with metastatic angiosarcoma involving the lung usually have an established diagnosis of malignancy at the time they present with hemoptysis and multiple nodules on chest radiographs. Diffuse pulmonary hemorrhage (DPH) is usually a life threatening condition characterized by widespread intra-alveolar hemorrhage. Classic clinical features include hemoptysis, anemia, and diffuse radiographic infiltrates. The most common causes are Goodpasture syndrome, vasculitides such as Wegener's granulomatosis and microscopic polyangiitis, and connective tissue diseases including systemic lupus erythematosus. The diagnosis is usually made on the basis of clinical, laboratory and radiologic findings.

Nine patients with metastatic angiosarcoma presenting with PH have been described in the peer-reviewed literature; table 13-1 summarizes these nine patients as well as seven additional patients whose lung biopsies were seen in consultation (including the patient under discussion). Patients are usually previously healthy young adults with no history of malignancy. The mean age of all reported patients is 40.1 years (median 33 years), and ten were less than 40 years of age. Men are affected more often than women by a ratio of 3 to 1. All affected women were less than 35 years of age at the time of diagnosis. None of the reported patients were known to have malignancy prior to lung biopsy or autopsy. Indeed, in three of our patients and six additional reported patients, the primary site was discovered only at autopsy, emphasizing the difficulty of identifying a primary site even after the diagnosis is established. The right atrium was the most common primary site, accounting for nine of eleven patients in whom a primary site was documented.

TABLE 13-1: SUMMARY OF 16 PATIENTS WITH PULMONARY METASTASES OF ANGIOSARCOMA PRESENTING AS DIFFUSE PULMONARY HEMORRHAGE

Reference	Age/Gender	Primary site / Method of diagnosis	Follow-up
Yousem, 1986	22/M	Unknown	DOD after one month
	28/W	Right atrium and ventricle / Ultrasound and CT-scans	AWD after 5 months
	30/W	Unknown	DOD after 3 weeks
Zwaveling, 1988	23/M	Right atrium / Autopsy	DOD 2 months post-diagnosis
Nara, 1996	33/W	Right ovary / Autopsy	DOD 8 weeks after presentation
Rajdev, 1978	35/M	Right atrium / Autopsy	DOD 8 months after presentation
Bic, 1994	43/M	Right atrium / Autopsy	DOD after 8 days
Ebi, 1997	47/M	Right atrium / Autopsy	DOD 7days post-hosp
Romero-Menor, 1995	65/M	Right atrium / Autopsy	DOD after 2 months
Adem (submitted)	NA/M	NA	NA
	31/M	Right atrium/ cardiac US	NA
	33/W	Not known (cardiac US "negative")	Lost to follow-up
	33/M	Right atrium/autopsy	DOD
	38/M	Right atrium/autopsy	DOD
	68/M	Base of penis/autopsy	DOD after 3 mos & 3 wks
	73/M	NA	NA

Pulmonary hemorrhage often overshadows other histologic findings in lung biopsies demonstrating metastatic angiosarcoma. Indeed, the initial pathologic diagnoses in two of our patients were Goodpasture syndrome and hemorrhagic pneumonitis. Accurate diagnosis hinges on recognition of atypical vasoformative spindled and epithelioid cells distributed in a distinctly lymphangitic pattern. Once the presence of neoplastic cells is recognized, the ***differential diagnosis*** includes other vascular neoplasms (*e.g.* epithelioid hemangioendothelioma and Kaposi sarcoma) and angiomatous variant of metastatic carcinoma (see Table 13-2). *Epithelioid hemangioendothelioma* is frequently distributed in a lymphangitic and endovascular pattern, but the epithelioid cells are cytologically bland and grow in a chondroid or myxoid stroma (see Case 5 for more detailed discussion). Distinguishing pulmonary *Kaposi sarcoma* from metastatic angiosarcoma can be exceedingly difficult, since both show a similar predilection for lymphatic pathways. Kaposi sarcoma usually occurs in patients with underlying AIDS, and the bland spindle cell proliferation usually shows no neoplastic vascular spaces. Metastatic carcinoma enters the differential diagnosis as well. Indeed, so-called *pseudoangiomatous carcinomas* can closely mimic the vasoformative growth pattern of angiosarcoma, while epithelioid angiosarcoma can mimic the solid growth pattern and cytologic characteristics of poorly differentiated carcinomas. In difficult cases, immunohistochemical stains can resolve the issue since carcinomas are immunoreactive for cytokeratin and fail to stain for endothelial-associated markers such as factor VIII-related protein and CD31.

TABLE 13-2: DIFFERENTIAL DIAGNOSIS OF METASTATIC ANGIOSARCOMA

	Metastatic Angiosarcoma	Epithelioid hemangio-endothelioma	Kaposi sarcoma	Metaplastic carcinoma
Clinical features	Young men	Women	AIDS	Smokers, 5th to 6th decade
Morphologic features	Lymphangitic or endovascular growth pattern of neoplastic cells, with vascular channel formation.	Bland neoplastic cells in a chondroid or myxoid stroma	Malignant proliferation without anastomosing vascular spaces. Presence of intra and extra cytoplasmic eosinophilic bodies, and extravasated red cells	Pseudo-vascular channel formation, in a lymphangitic growth pattern.
CD31-Factor VIII Immunostains	Positive	Positive	Positive	Negative

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Case #14

Clinical history - Acc. # 28198

A 51-year-old man was discovered to have a mass in the left lower lobe. Fiberoptic bronchoscopy demonstrated no endobronchial disease. He underwent thoracotomy and left lower lobectomy. Examination of the resected lobe showed a solid 6 cm mass confined to the lung with no pleural involvement. (Contributed by Roger Terry, M.D., San Gabriel, CA)

Diagnosis: *Solitary Fibrous Tumor*

Discussion:

Localized (solitary) fibrous tumors of the pleura (formerly referred to as "fibrous mesotheliomas") are mesenchymal neoplasms derived from subpleural connective tissue. Localized fibrous tumors are not unique to the pleura, however, and have been described in nearly all extrapleural sites including lung, mediastinum, extrapleural serosal surfaces (*i.e.* pericardium, peritoneum, tunica vaginalis, spermatic cord), nose and paranasal sinuses, pharynx, soft tissues, parapharyngeal space, epiglottis, salivary glands, meninges, orbit, retroperitoneum, liver, thyroid, and breast. Intrapulmonary localized fibrous tumors are histologically and immunophenotypically indistinguishable from the more common localized fibrous tumor of the pleura, differing only in being confined to the lung parenchyma.

Localized fibrous tumors of the pleura affect both males and females with no sex predilection. Most are discovered in middle aged or older adults although examples have been reported in patients as young as 9 years of age. The majority of patients present with asymptomatic intrathoracic masses. Symptomatic patients comprise a minority and present with nonspecific complaints including chest pain, cough, and shortness of breath. Clubbing is uncommon. An unusual syndrome of tumor-related hypoglycemia has also been described. Patients with intrapulmonary localized fibrous tumors are similar to patients with pleural tumors and typically present with asymptomatic solitary pulmonary nodules.

Grossly, localized fibrous tumors are circumscribed firm, rubbery masses that most commonly arise from visceral pleura. Many are pedunculated and are connected to the pleural surface by a connective tissue pedicle. Histologically, localized fibrous tumors are variably cellular spindle cell neoplasms with a collagenous stroma. The spindle cells are arranged in a variety of growth patterns ranging from a so-called "patternless pattern" to a vascular mesenchymal pattern resembling hemangiopericytoma. Nuclear palisading can also occur and can mimic the appearance of neurilemmoma. As with pleural tumors, most behave as benign neoplasms and are cured with complete surgical excision. A minority of cases pursue a more aggressive course and are distinguished by being more cellular with higher mitotic rates, necrosis, and vascular invasion. Malignant intrapulmonary localized

fibrous tumors overlap histologically with other forms of sarcoma including malignant hemangiopericytoma and fibrosarcoma.

Immunohistochemical studies are relatively nonspecific with positive staining for vimentin and negative staining for keratins, S100 protein, and muscle markers (Table 14-1). CD34 staining has been demonstrated in the majority of localized fibrous tumors from a variety of pleural and extrapleural sites. Positive CD34 staining is not specific, however, and has been shown in other soft tissue neoplasms including hemangiopericytoma.

TABLE 14-1: IMMUNOSTAINING RESULTS IN 61 CASES* OF LOCALIZED (SOLITARY) FIBROUS TUMOR

Antigen	No. pos/total tested
CD34	51/61 (83.6%)
MSA	1/42 (2.4%)
SMA	1/42 (2.4%)
Desmin	4/39 (10.3%)
Keratin (AE1; AE1/1E3; CAM5.2)	1/58 (1.7%)
CD15 (leuM1)	0/7
S100 protein	0/6
NSE	10/27 (37.0%)
Chromogranin	0/15

*data summarized from van de Rign et al. Am J Surg Pathol 1994; 18: 814; Hanau & Miettinen. Hum Pathol 1995; 26: 440; and Flint & Weiss. Hum Pathol 1995; 26: 428.

The ***differential diagnosis*** is limited and includes other benign or low grade spindle cell neoplasms. So-called *inflammatory pseudotumors* represent a heterogeneous group that generally lack the spindle cell proliferation that characterizes localized fibrous tumors, showing instead broad zones of dense collagen deposition. *Plasma cell granulomas* (also termed fibrous histiocytomas, inflammatory myofibroblastic tumors, inflammatory myofibrohistiocytic proliferations, and included by some with inflammatory pseudotumors) tend to have a more fibrohistiocytic appearance with an inconstant mononuclear inflammatory infiltrate including plasma cells and histiocytes. The neoplastic spindle cells of plasma cell granulomas are vimentin positive and also stain for muscle markers (actin and desmin) with negative staining for CD34. At the more malignant end of the spectrum, localized fibrous tumors overlap with *malignant fibrous histiocytomas* and other forms of *sarcoma*. Recognition of areas with the heterogeneous patterns of localized fibrous tumors can be helpful in difficult cases, although precise classification of malignant tumors is of doubtful clinical significance. Malignant tumors should be distinguished from *sarcomatoid carcinomas* which can occasionally have a deceptively bland appearance. Keratin stains are helpful in distinguished spindle cell carcinomas from other spindle cell lesions, such as localized fibrous tumors.

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Case #15

Clinical History - Acc. # 29164

A 58-year-old man underwent lobectomy for a persistent cavitary mass situated in the right upper lobe. While awaiting surgery he developed a destructive sinusitis. Urinalysis and renal function were within normal limits. (Contributed by Laila Chandy, Sacramento, CA)

Diagnosis: *Wegener's Granulomatosis*

Discussion:

Wegener's granulomatosis is a vasculitic syndrome of unknown etiology with protean clinical manifestations. The broad clinical spectrum of disease ranges from relatively mild smoldering illness to fulminant respiratory and renal failure characterized by an explosive onset and a rapidly fatal course. Classical Wegener's granulomatosis involves the lungs, kidneys and upper respiratory tract. Limited Wegener's granulomatosis involves only the lungs without associated glomerulonephritis or upper respiratory tract disease. Numerous other sites (*e.g.* skin, breast, salivary glands, prostate gland, temporal artery) can also be involved. Patients with lung involvement are usually symptomatic and complain of cough, hemoptysis, dyspnea, and/or fever. Chest radiographs are variable but usually show multiple nodules, frequently with central cavitation.

Antineutrophil cytoplasmic autoantibodies (ANCA) with specificity for proteinase-3 (c-ANCA) are relatively specific for Wegener's granulomatosis and represent the single most important addition to laboratory analysis of patients suspected of having Wegener's granulomatosis. C-ANCA titers are positive in about 90% of patients with active generalized disease, 60 to 85% of patients with active localized disease, and 30 to 35% of patients with quiescent disease. Thus, serum c-ANCA titers can be used not only as a diagnostic tool, but also to monitor disease activity in patients with established diagnoses of Wegener's granulomatosis. Positive p-ANCA titers, generally representing autoantibodies directed against myeloperoxidase, are less specific but are positive in some patients with Wegener's granulomatosis.

Lung biopsy findings in Wegener's granulomatosis are as variable as the clinical manifestations of the illness. Stereotypical cases comprise a combination of necrotizing granulomatous inflammation and necrotizing vasculitis. Broad geographic zones of necrosis surrounded by a polymorphic inflammatory infiltrate that includes palisaded histiocytes and multinucleated giant cells characterize the necrotizing granulomatous inflammation. The central necrosis has a characteristic "dirty" granular appearance resulting from karyorrhexis and lysis of neutrophils ("nuclear dust"). Multinucleated giant cells also have a characteristic darkly staining and smudged appearance. The vasculitis involves arteries and veins of various sizes as well as capillaries ("capillaritis"). The nature of the vascular

infiltrate is variable, ranging from necrotizing granulomas to fibrinoid necrosis with neutrophils. The vascular changes tend to be punctate and focal, and can easily be missed with inadequate sampling.

Some authors have focused attention on a peculiar form of necrosis ("pathergic necrosis") as the sentinel lesion of Wegener's granulomatosis. According to proponents of this viewpoint, the initial lesion is necrosis of stromal collagen followed by a neutrophilic infiltrate with formation of granulomatous microabscess which expand and coalesce to form broad zones of geographic necrosis with palisaded histiocytes and multinucleated giant cells. The granulomatous microabscesses emphasized in this theory of pathogenesis are a frequent finding in Wegener's granulomatosis and can be a helpful clue to the diagnosis.

Several histopathological variants of Wegener's granulomatosis have been described and emphasize the protean manifestations of this unique syndrome. The eosinophilic variant differs only in that the mixed inflammatory background includes prominent numbers of eosinophils. Affected patients usually do not have peripheral eosinophilia or asthma, and show clinical and radiographic findings typical of Wegener's granulomatosis. Airway involvement can be the predominant finding in some patients and can mimic bronchocentric granulomatosis, a nonspecific pattern of bronchocentric or bronchiolocentric granulomatous inflammation seen in a wide variety of conditions. Pulmonary hemorrhage with capillaritis is a well described manifestation of Wegener's granulomatosis and tends to be associated with a rapidly progressive course resembling Goodpasture's syndrome. Demonstration of concomitant c-ANCA titers and anti-glomerular basement membrane autoantibodies in some patients with pulmonary-renal syndrome suggest that there may be a certain degree of overlap between these conditions. Katzenstein and colleagues called attention to yet another histological variant of Wegener's granulomatosis in which a pattern of intraluminal fibrosis resembling cryptogenic organizing pneumonia (BOOP) is the dominant finding.

In its classic form, Wegener's granulomatosis is easily recognized in open lung biopsies. The main ***differential diagnosis*** is *granulomatous infection* which should be excluded with appropriate special stains and cultures. Well formed sarcoid-like granulomas are unusual in Wegener's granulomatosis and, if present, are likely to indicate granulomatous infection. Separation of the eosinophilic variant of Wegener's granulomatosis from *Churg-Strauss syndrome* (allergic angiitis and granulomatosis) can usually be done on the basis of clinical findings: patients with Churg-Strauss syndrome invariably have underlying asthma, peripheral eosinophilia, and are more likely to have positive p-ANCA titers rather than c-ANCA titers. Diffuse alveolar hemorrhage with capillaritis is not specific and can be seen in conditions other than Wegener's granulomatosis (*e.g.* systemic lupus erythematosus). Distinguishing these conditions frequently requires correlation with other laboratory tests, particularly the presence or absence of c-ANCA titers.

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Case #16

Clinical history - Acc. # 20932

A 69-year-old man was discovered to have a left lung mass on chest x-ray. He underwent thoracotomy and left lower lobectomy. The cut surface of the lobectomy specimen demonstrated "5 discrete, scattered, circumscribed but unencapsulated, tan-yellow nodules and a cluster of coalescing nodules at the hilum". (Contributed by Robert Silton, M.D., Duarte, CA)

Diagnosis: ***Lymphomatoid Granulomatosis (Diffuse Large B-Cell Lymphoma, Lymphomatoid Granulomatosis-type)***

Discussion:

Liebow and colleagues first described pulmonary lymphomatoid granulomatosis (LYG) as a distinct clinicopathologic entity in 1972. It was defined as an angiocentric lymphoproliferative process with prominent pulmonary involvement. As originally described, the diagnosis hinged on recognition of a characteristic histologic triad: 1) polymorphic lymphoid infiltrate, 2) angiitis, and 3) "granulomatosis". The most distinctive feature was the presence of a polymorphic mononuclear cell infiltrate composed of small lymphocytes, plasma cells, and variable numbers of large immunoblasts. Angiitis was a consistent finding characterized by transmural infiltration of the walls of arteries and veins by mononuclear cells. The term "granulomatosis" was used to describe the necrosis occurring within the lymphoid nodules rather than true granuloma formation.

The intimate relationship between LYG and malignant lymphoma was well recognized from the outset. The original authors balked at designating the condition lymphoma because most patients lacked nodal disease, the liver and spleen were rarely involved, occasional patients spontaneously recovered, and the polymorphic nature of the infiltrate defied existing histological criteria for diagnosis of lymphoid malignancy. Recognition and study of extranodal lymphomas over the last two decades has explained some of the "deviant characteristics" of LYG and there is now little doubt regarding the neoplastic nature of this lesion.

LYG has characteristic clinical features. Males are affected more often than females by a ratio of 2-3:1; patients usually present in the fifth or sixth decade of life. Respiratory symptoms, most commonly cough, occur in the majority of patients and are frequently associated with systemic complaints such as fever and weight loss. Extrathoracic manifestations are common and include skin involvement in 37% and central or peripheral nervous system involvement in 30% of patients. Chest roentgenograms typically show bilateral discrete rounded nodules which may show cavitation. Intrathoracic adenopathy is rare as is peripheral adenopathy. Traditionally, LYG-lymphoma has carried a poor prognosis with a cumulative mortality of 57% in the two largest retrospective series. Recent

experience suggests that aggressive chemotherapy substantially improves survival. Wilson and colleagues reported success in 4 patients using interferon-α2b as a single agent, and suggested further investigation of antiviral/immunomodulating drugs in this condition.

Historically many examples of LYG were thought to represent T-cell lymphomas. Prior to 1994, most cases of LYG had been analyzed using frozen section immunostaining techniques and showed a mature T-cell phenotype, characteristic of so-called peripheral T-cell lymphomas. An aberrant T-cell phenotype had been demonstrated in a few cases, although clonal rearrangements of the T-cell receptor gene had been documented only rarely and never in lung tissue. Importantly, clonal T-cell receptor gene rearrangements were usually not identified, even in some cases with aberrant T-cell phenotypes and in one with a cytogenetically abnormal clone.

Most cases of LYG are now thought to represent EBV-related B-cell lymphoproliferative disorders with an exuberant reaction of non-neoplastic T lymphocytes. Guinee and colleagues demonstrated a minor population of EBV-infected CD20 positive B lymphocytes in biopsies of LYG, and a monoclonal pattern of immunoglobulin heavy chain gene rearrangements was found in two thirds. They concluded that most cases of LYG involving the lung represent examples of EBV related B-cell lymphoproliferative disorders with a prominent component of reactive T lymphocytes. We reported our own experience with 17 open lung biopsies from patients with LYG and observed a predominance of T lymphocytes in all cases. Our findings differed somewhat from Guinee et al., however, in that a minor population of CD20-positive large B lymphocytes was identified in only 11 cases; immunoglobulin light chain restriction was demonstrated in 4 of these, and immunoglobulin gene rearrangements in another. Staining for CD20 was absent in the remaining 6 cases; however, the large atypical lymphoid cells stained for T-cell lineage specific antibodies in 3 of these cases. We concluded that some cases of LYG are B-cell lymphomas analogous to so-called "T-cell rich B-cell lymphomas" while others may represent T-cell lymphomas. Several authors have now confirmed the unique "T-cell rich B-cell" phenotype that characterizes the majority of cases of LYG and have demonstrated that most represent monoclonal or oligoclonal proliferations of B lymphocytes (see Table 16-1).

TABLE 16-1: LYMPHOMATOID GRANULOMATOSIS -- AN EBV-RELATED B-CELL LYMPHOMA

	N	CD20+ lge cells	EBV+ cells	clonal
Guinee et al.	10	10	10	6
Myers et al.	17	11	10	5
McNiff et al.	4	4	3	4
Nicholson et al.	7	7	4	3
Wilson et al.	4	4	4	2
TOTAL	**42**	**36**	**31**	**20**

A number of other studies of LYG have shown a link to EBV infection. Liebow and colleagues theorized an etiologic role for EBV and even suggested that ". . . studies analogous to those that have led to the identification of a virus associated with Burkitt's lymphoma should be performed in lymphomatoid granulomatosis." Katzenstein and Peiper identified EBV viral DNA sequences in lung biopsies of LYG using the polymerase chain reaction. Southern blotting and in-situ hybridization techniques have also demonstrated EBV sequences in LYG, particularly those cases with cytologically malignant large lymphoid cells. Although Medeiros and colleagues using double labeling techniques suggested that EBV infected cells represented neoplastic T-cells, subsequent studies by Guinee et al. demonstrated EBV genomes in CD20 positive B lymphocytes. In our own study we demonstrated nuclear labeling for EBV RNA in 10 of 11 cases with CD20-positive B cells, and the staining was confined to the population of large B lymphocytes. Nuclear labeling for EBV RNA was absent in 6 cases lacking CD20-positive large cells.

The most appropriate terminology for LYG remains problematic. None of the classification schemes currently employed for malignant lymphomas have a suitable nosological category for LYG. As a result several synonyms have been proposed to replace the term lymphomatoid granulomatosis. The currently proposed WHO classification of hematopoetic and lymphoid neoplasms applies the term, "diffuse large B-cell lymphoma, lymphomatoid granulomatosis-type." Jaffe previously coined the term *angiocentric immunoproliferative lesion (AIL)* to encompass a spectrum of lymphoproliferative disorders ranging from low grade lesions of uncertain histogenesis (grade I AIL) to high grade angiocentric lymphomas (grade III AIL). Katzenstein and Askin suggested the term *lymphomatoid granulomatosis-lymphoma*, which has the advantages of emphasizing that LYG is a malignant neoplasm while preserving the historical context of this unique clinicopathological syndrome and separating it from other forms of malignant lymphoma. Whatever terminology one prefers, including in some fashion the term LYG for descriptive purposes may be useful to emphasize the unique clinical and pathological features of this lesion.

The ***differential diagnosis*** of LYG-lymphoma in lung biopsy specimens includes mainly Wegener's granulomatosis and other forms of malignant lymphoma. *Wegener's granulomatosis* differs from LYG-lymphoma in that the cellular infiltrate is composed of acute and chronic inflammatory cells and the vasculitis consists of focal vessel wall necrosis rather than transmural infiltration by lymphoid cells. *Other forms of malignant lymphoma*, including Hodgkin's disease and non-Hodgkin's lymphomas, can involve the lung and show histologic features that overlap with LYG-lymphoma. Recognition of Hodgkin's disease requires identification of diagnostic Reed-Sternberg cells as it does in extrapulmonary sites. Distinguishing LYG-lymphoma from other types of non-Hodgkin's lymphomas is more problematic. The term LYG-lymphoma should be reserved for those cases with the histologic triad initially outlined by Dr. Liebow et al: a polymorphic lymphoid infiltrate, vascular infiltration, and necrosis. It is the presence of a polymorphic infiltrate in at least a portion of the tumor that is most useful in distinguishing LYG from other forms of pulmonary lymphoma. Vascular infiltration alone is an insufficient criterion because it can occur in other types of malignant lymphoma. Ultimately, of course, recognition of LYG as

a distinct clinicopathologic entity requires careful correlation of biopsy findings with clinical, radiographic, and now immunophenotypic data.

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Case #17

Clinical history - Acc. # 24262

A 73-year-old woman, a retired school teacher, presented for evaluation of a suspicious mass in the right mid lung field. She had been evaluated two years previously for a suspicious left-sided density seen on chest x-ray. Mediastinal biopsy at that time showed no evidence of tumor. The current lesion was discovered one month prior to surgery and had persisted despite antibiotic therapy. She underwent thoracotomy and right middle lobectomy. The resected lobe showed a solitary 3.5 cm rubbery, tan homogeneous lesion beneath the pleural surface that irregularly infiltrated the surrounding lung parenchyma. (Contributed by P. L. Morris, M.D., Santa Barbara, CA)

Diagnosis: *Extranodal Marginal Zone B-Cell Lymphoma of MALT-type*

Discussion:

A number of lymphoproliferative diseases, including benign and malignant disorders, may involve the lung primarily (Table 17-1).

TABLE 17-1: CLASSIFICATION OF PULMONARY LYMPHOPROLIFERATIVE DISORDERS

Benign lymphoproliferative disorders
- Lymphoid hyperplasia
  - intrapulmonary lymph nodes
  - follicular bronchitis/bronchiolitis
  - diffuse lymphoid hyperplasia
- Pseudolymphoma (localized/nodular lymphoid hyperplasia)
- Lymphoid interstitial pneumonia

Malignant lymphoproliferative disorders
- Non-Hodgkin's lymphoma
  - Extranodal marginal zone B-cell lymphoma of MALT type
  - Intermediate/high grade lymphoma
    - Lymphomatoid granulomatosis-lymphoma (LYG)
    - Intravascular lymphomatosis
- Hodgkin's disease
- Secondary pulmonary lymphoma/leukemia
- Miscellaneous conditions

Posttransplant lymphoproliferative disorders
- Lymphoid infiltrates in other immunocompromised patients

Extranodal marginal zone B-cell lymphoma of MALT type (low grade lymphoma of MALT)

Low grade lymphoma accounts for over 80 per cent of primary pulmonary lymphomas. Low grade lymphomas of the lung comprise a relatively homogeneous group: the majority represent low grade extranodal marginal zone B-cell lymphomas of MALT type analogous to those described in other sites. Low grade pulmonary lymphomas usually occur in adults, with a mean age of onset in the sixth decade of life. Women are affected slightly more often than men are by a ratio of 1.2:1. As many as a third to over half of patients are asymptomatic at the time a radiographic abnormality is discovered. Symptomatic patients have nonspecific respiratory complaints of cough and dyspnea, occasionally associated with chest pain or hemoptysis. Weight loss and fever accompany the respiratory complaints in some patients. Sjogren's syndrome is seen in about 10 per cent of patients and usually precedes the diagnosis of lymphoma by several years. Laboratory studies demonstrate a monoclonal gammopathy in about a third of patients, usually of IgM type. Indeed, Waldenstrom's macroglobulinemia can antedate or follow the diagnosis of pulmonary involvement by low grade lymphoma.

Radiographic findings in primary pulmonary lymphomas are not specific. Over two thirds of patients have solitary pulmonary nodules or localized air space opacities at the time of presentation. Opacities due to lymphoma tend to be larger than those seen in pulmonary pseudolymphoma, averaging 6.2 cms and measuring up to 12 cms in the experience of Julsrud et al. Multiple nodules or air space opacities are seen in about 25 per cent of patients. Diffuse interstitial infiltrates are distinctly unusual in primary pulmonary lymphoma and may be more common in patients with underlying Sjogren's syndrome. Pleural effusion and intrathoracic adenopathy are present in only a small number of patients. Exquisite localization to the tracheobronchial tree is seen in some patients and can cause lobar atelectasis or collapse. Tracheobronchial involvement can take the form of discrete exophytic nodules (solitary or multiple) or diffuse infiltration of the submucosa.

Low grade lymphomas of the lung are associated with an excellent prognosis. Staging studies indicate that most patients have disease confined to the lung. Intrathoracic lymph node involvement is uncommon and bone marrow involvement is rare. Paraproteinemia has been associated with a worse prognosis in some studies. Over half of patients achieve complete remission after surgical excision or immunosuppressive therapy. Another 25 per cent of patients will have stable non-progressive disease over long periods of observation, and about 10 per cent of reported patients have died of other or unknown causes. Only about 5 per cent of patients ultimately succumb to their disease, usually after survivals of several years.

The histological findings in low grade lymphoma are distinctive and most cases can be diagnosed on the basis of routinely stained sections alone. At low magnification the main change is the presence of a dense lymphoid infiltrate with, at least focally, an exquisitely lymphangitic distribution. The lymphoid infiltrate is accentuated along bronchovascular bundles, interlobular septa, and visceral pleura. In contrast to diffuse lymphoid hyperplasia, the infiltrate is expansive and forms scattered microscopic or macroscopic nodules that obscure the underlying lung structures. Lymphoepithelial complexes involving bronchiolar

epithelium are present in some cases but are not usually a prominent finding, and also occur in conditions other than malignant lymphomas. Involved bronchoalveolar bundles may show vascular infiltration ("angiitis") and/or evidence of destructive invasion of bronchial cartilage. At higher magnification the lymphoid infiltrate is relatively monomorphic and is composed of small lymphocytes with rounded nuclei and "centrocyte-like" cells with slightly irregular nuclear contours and scant or clear cytoplasm. Plasmacytic differentiation is seen in about a third of cases and includes the presence of plasmacytoid lymphocytes and mature plasma cells. PAS-positive intranuclear inclusions (Dutcher bodies) are present in some cases. Dutcher bodies are much more commonly associated with lymphomas than reactive lymphoid infiltrates and can be a helpful feature in distinguishing low grade lymphoma from benign conditions. Synchronous or metachronous transformation to large cell lymphoma has been described in as many as 10 to 15 per cent of cases and probably implies a worse prognosis.

Secondary changes are frequently seen in small lymphocytic lymphomas and may cause difficulties in diagnosis. Germinal centers do occur and can be a prominent feature in occasional cases but are usually infrequent and small. Immunophenotyping studies have demonstrated monoclonal neoplastic lymphocytes encroaching upon benign polyclonal germinal centers in well documented examples of lymphoma. Patchy areas of organizing intraluminal fibrosis are seen in some cases and may be confused with organizing pneumonia or bronchiolitis obliterans organizing pneumonia (BOOP). The key to diagnosis is recognition of the underlying lymphoid infiltrate with a lymphangitic distribution. Non-necrotizing granulomas can also occur, particularly in patients with underlying Sjogren's syndrome, and can mimic granulomatous infection, hypersensitivity pneumonia, or sarcoidosis. Again, distinguishing these conditions depends on recognition of a prominent monomorphic lymphoid infiltrate with a distribution more typical of lymphoma. Amyloid is an uncommon finding in low grade lymphomas of the lung and can take the form of either diffuse alveolar septal or nodular amyloidosis.

PRIMARY PULMONARY EXTRANODAL MARGINAL ZONE LYMPHOMA of MALT TYPE

KEY LIGHT MICROSCOPIC FEATURES

- **low magnification**
  - mass-like growth forming nodules
  - "lymphangitic" distribution
- **high magnification**
  - monomorphic population of small lymphocytes +/- plasmacytic differentiation
  - lymphoepithelial lesions

The main ***differential diagnosis*** for small lymphocytic lymphoma includes benign lymphoproliferative disorders (*pseudolymphoma, diffuse lymphoid hyperplasia, lymphoid interstitial pneumonia*) (Table 17-2). Special diagnostic techniques can be extremely useful in difficult cases. Nearly all cases represent B-cell neoplasms. Paraffin section immunostains are especially helpful in cases showing plasmacytic differentiation and demonstrate cytoplasmic immunoglobulin light chain restriction. However, reactive plasmacytosis can accompany B-cell lymphomas in the lung, so demonstrating polytypic plasma cells in a suspicious lymphoid infiltrate does not exclude the diagnosis of lymphoma. Fresh tissue for frozen section immunostains or molecular genetic analysis is helpful in those cases that lack plasmacytic differentiation. It should be emphasized, however, that most cases can be resolved on the basis of routine histology.

TABLE 17-2: DIFFERENTIAL DIAGNOSIS OF SMALL LYMPHOCYTIC LESIONS OF THE LUNG (PSEUDOLYMPHOMA, LYMPHOID INTERSTITIAL PNEUMONIA, LOW GRADE LYMPHOMA)

	Pseudolymphoma	LIP	Lymphoma
CLINICAL FEATURES			
Mean age	6th decade	5th-7th decade	6th decade
Resp symptoms	±	+	±
Extrapulmonary lymphocytic infiltrate	-	±	±
Assoc with Sjogren's Syndrome	+	+	+
Chest x-ray			
solitary nodule/opac	+	-	+
mult nod/opac	±	+	+
diffuse infilt	-	+	±
adenopathy	-	-	±
PATHOLOGICAL FEATURES			
Distribution	solitary nodule	diffuse interstitial	lymphangitic
Visc pleural invasion	rare	rare	common
Bronchial cart invasion	rare	rare	common
Germ centers	common	common	uncommon, prominent in rare cases
Lymphoepithelial complexes	-	-	+
Cytology	polymorphic	polymorphic	monomorphic
Dutcher bodies	-	-	+
Immunophenotype	polyclonal	polyclonal	monoclonal, B-cell

Malignant lymphomas of follicular center cell origin are distinctly uncommon among primary pulmonary lymphomas, representing only 15 per cent of the 121 low grade lymphomas reported by Koss et al. Most form destructive tumorous masses and have a diffuse growth pattern, although a follicular growth pattern occasionally occurs in primary pulmonary tumors. Nonetheless, recognition of a follicular center cell lymphoma in the lung should prompt a careful search for evidence of extrapulmonary disease.

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Case #18

Clinical history - Acc. # 29165

A 35-year-old woman was first seen at Mayo Rochester in November of 1990 for evaluation for single lung transplantation. Her chief complaint was a 7 to 8 year history of progressive shortness of breath. In addition she complained of frequent upper respiratory tract infections associated with productive cough. Her symptoms had accelerated over the year prior to evaluation. PFTs showed severe restriction (FEV1 0.45 liters; FEV1/FVC 25.1). A chest x-ray showed a diffuse interstitial process with hyperinflation. She was listed for transplantation and underwent orthotopic lung transplantation in January of 1992.

Diagnosis: *Lymphangioleiomyomatosis*

Follow-up: She is doing well, with no evidence of recurrent disease in her transplanted lung, 8 years after transplantation.

Discussion:

Lymphangioleiomyomatosis (LAM), also called lymphangiomyomatosis, is a rare condition that affects women almost exclusively, usually in the reproductive age group. The classic clinical triad is diffuse interstitial lung disease, recurrent pneumothoraces, and chylous pleural effusions. Hemoptysis is also a common presenting complaint. Physiologic testing demonstrates airflow obstruction with air trapping associated with disproportionately severe hypoxemia and reduction in DL_{CO}. Chest radiographs are normal early in the course of the illness, but eventually show diffuse interstitial opacities, cystic spaces resembling honeycomb change, and paradoxical lung enlargement. This constellation of findings is said to be pathognomonic of this condition. High resolution CT scans show characteristic changes and can be extremely useful in diagnosis. LAM traditionally has been considered a relentlessly progressive disorder with a poor prognosis. A review of 32 patients reported from the Mayo Clinic by Taylor and colleagues suggested that as many as 80% of patients may survive for ten years or more, with most respiratory deaths occurring within five years of diagnosis. Two recently published series with large numbers of French and U.S. patients showed similar survival rates. Others report a less favorable prognosis. Progestogen therapy has proven most effective in treating this condition, although various other hormonal manipulations have been attempted with varying degrees of success. LAM is also an indication for lung transplantation, but can recur in lung allografts.

The main pathologic abnormality in LAM is a disorderly proliferation of specialized smooth muscle cells along lymphatic pathways with extension into bronchiole walls, veins, and small air spaces. The proliferating cells tend to be spindled in shape, although plump epithelioid forms also occur and can predominate in some cases. Spindle and epithelioid cells frequently coalesce to form nodules. Cystic "emphysematous" spaces are common especially in advanced disease, and usually contain smooth muscle bundles within at least a

portion of their walls. The presence of these cystic spaces may be the first clue to the diagnosis at low magnification. Hemosiderin often is present within surrounding air spaces, particularly in advanced or late stage disease, and attests to pulmonary hemorrhage in these patients. A recent review indicates that semiquantitative histologic assessment of disease severity based on the extent of cystic change combined with smooth muscle proliferation may have value in identifying prognostically different subgroups.

The modified smooth muscle cells of LAM are likely derived from perivascular epithelioid cells. Immunostaining results have shown features consistent with smooth muscle differentiation, including consistent expression of sex steroid receptors. Perhaps the most distinctive and compelling feature of the specialized smooth muscle cells in LAM is consistent expression of melanogenesis-associated proteins, most commonly HMB45. Melan-A is a less sensitive marker for this condition. HMB45 can be a helpful diagnostic marker in difficult cases such as small transbronchial biopsies. A subset of LAM cells are positive with antibodies for matrix metalloproteinases and their activators indicating that these may play a role on the elastic fiber degradation that contributes to the cystic change. Recent immunohistochemical studies using confocal microscopy suggest that there may be immunophenotypically distinct subpopulations of small spindle cells and larger epithelioid cells as summarized in the table. This dimorphic population of lesional cells is not usually apparent in routine histologic preparations, and the significance of these observations is uncertain. With the exceptions of smooth muscle actin and HMB-45, frequency of immunoreactivity is diminished after hormonal treatment.

TABLE 18-1: IMMUNOPHENOTYPE OF PUTATIVE CELL SUBSETS IN LAM

Antigen	Epithelioid cells	Spindle cells	Immunoreactivity diminished after treatment?
SMActin	+	+	No
HMB45	+	-	No
ER/PR	+	-	Yes
PCNA	↓	↑	Yes
MMP-2	+	+	?*
MT-1-MMP	-	+	Yes

* immunostains with mouse monoclonal (vs. rabbit polyclonal) diminished with treatment

LAM is related to tuberous sclerosis complex (TSC), a multisystem autosomal dominant disorder characterized by the presence of hamartomatous tumors in various organs, most commonly skin, brain, heart and kidney. About 1-3% of patient with TSC have lung involvement that is morphologically indistinguishable from sporadically occurring LAM. Patients with TSC and LAM are interesting in that they tend to be women of reproductive age without CNS stigmata of TSC and thus resemble other patients with LAM. The single exception is a recently reported example of LAM in a man with underlying TSC. A recent report suggests that as many as 28% of women with TSC may have pulmonary LAM. The relationship between LAM and TSC is further complicated by demonstration of

renal angiomyolipomas in nearly 60% of patients with otherwise sporadic LAM. Recent observations suggest that there may be common genetic events in LAM and the other hamartomatous and neoplastic manifestations of TSC.

Micronodular pneumocyte hyperplasia (MNPH) is another manifestation of lung disease in patients with underlying TSC or sporadically occurring LAM. MNPH comprises circumscribed proliferations of cytologically bland type 2 pneumocytes in a pattern resembling bronchioloalveolar adenocarcinoma. Popper and colleagues coined the term MNPH to call attention to this epithelial proliferation involving the lungs of a 38 year old woman with TSC and LAM. Spencer and subsequently Corrin and colleagues had previously illustrated identical lesions in patients with TSC and LAM, respectively. More recently Muir et al. reported a series of 14 patients with MNPH, including nearly all previously reported examples. Ten (71.4%) of their patients, all women, had associated LAM and seven of these had other manifestations of TSC. Two additional patients had TSC without evidence of LAM, including one man (24 years of age). Two patients had MNPH as an isolated finding without TSC or LAM, and one of these was also a man (57 years of age). The recently reported example of LAM in a man with underlying TSC was also associated with MNPH. Indeed the combination of LAM and MNPH in a lung biopsy should be viewed as strong evidence in support of a diagnosis of TSC in a patient of either gender.

The ***differential diagnosis*** of LAM is limited. So-called *benign metastasizing leiomyoma* is a rare condition characterized by the presence of multiple circumscribed nodules of cytologically bland smooth muscle cells within the lungs. The nodules differ from the lesions of LAM in that they are usually solid and well circumscribed, and frequently have a "biphasic" appearance due to the presence of entrapped alveolar epithelial cells. Hemosiderin pigment deposition can be a prominent feature of LAM and may lead to confusion with *pulmonary hemorrhage syndromes*, particularly idiopathic pulmonary hemosiderosis. The presence of cystic spaces coupled with foci of neoplastic spindled cells in LAM should serve to distinguish these conditions.

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Case #19

Clinical History - Acc. # 29222

A 10-month-old boy was referred for a second opinion regarding the need for left upper lobectomy. He was the healthy product of an uncomplicated full term pregnancy. He gained weight normally and achieved normal developmental milestones. At several months of age the family noted that he was breathless and grunted with most activity. A diagnosis of asthma was made and he was started on Albuterol. A chest x-ray obtained for persistent symptoms one week prior to admission showed bilateral pulmonary cystic disease. A CT scan confirmed the presence of "multiple large bullae with internal septation involving both lungs." The changes involved mainly the lingula, anterior segment of the left upper lobe, and two basal segments of the right lower lobe. Preoperative considerations included congenital lobar emphysema and histiocytosis X. A left thoracotomy was performed.

Diagnosis: *Pleuropulmonary Blastoma*

Follow-up: The patient returned to the operating room one week later for right thoracotomy and removal of a histologically identical cystic mass occupying the lower half of the right hemithorax. He received combination chemotherapy elsewhere and returned four months later for repeat thoracotomy to evaluate persistent cystic disease in the left hemithorax. No evidence of persistent/recurrent tumor was identified.

Discussion:

Spencer coined the term *pulmonary blastoma* to describe a rare form of biphasic lung neoplasm previously reported as *embryoma of the lung* (see Case 11). As classically described, these peculiar lung tumors are distinguished by a combination of primitive blastematous stroma and an epithelial component resembling developing fetal lung tubules. The result is a histological appearance reminiscent of that seen in Wilms' tumor. Paradoxically, these tumor occur mainly in adults and likely represent variants of carcinosarcoma or sarcomatoid carcinoma. Although occasional cases occur in younger patients, most examples of so-called pulmonary blastoma affecting patients under the age of 15 are distinctly different as illustrated by this case, and are now referred to as pleuropulmonary blastoma (PPB). The revised WHO classification scheme groups PPB with other non-epithelial, intrathoracic soft tissue tumors and defines it as,

> *"A cystic and/or solid sarcoma in which the cystic component is lined by benign metaplastic epithelium that may be ciliated."*

Dr. Manivel and colleagues first proposed PPB as a distinct and separate entity in a 1988 report of 11 children with primitive mesenchymal or sarcomatous intrathoracic tumors. All patients were less than 15 years of age (range 30 months to 12 years) with no sex predilection (5 boys, 6 girls). The most common presenting complaints were fever (10), chest (5) or abdominal (5) pain, respiratory distress (7) and cough (5). Tumors ranged in

size from 8 to 23 cms in greatest dimension, involving lung (6), pleura (8) and/or mediastinum (8) in various combinations. The most consistent histologic finding was a primitive appearing blastematous stroma arranged in alternating loose and compact zones. Spindle cells, scattered large cells with eosinophilic cytoplasm, bizarre pleomorphic and occasionally multinucleated cells, eosinophilic cytoplasmic inclusions, focal erythropoiesis, and myxoid change were seen in various combinations resulting in a somewhat heterogeneous appearance. Histologic features of rhabdomyosarcoma were identified at least focally in all cases, and cells in these areas were consistently immunoreactive for both desmin and myoglobin. Focal cartilaginous differentiation was seen in three cases. Incorporated non-neoplastic respiratory epithelium resulted in a biphasic pattern in some patients. Nine patients developed recurrent or metastatic disease, and seven died of disease 5 month to 2 years after diagnosis. Four were alive with no evidence of disease up to 12 years after diagnosis. The authors concluded that PPB is a discrete clinicopathologic entity that is analogous to other embryonic-fetal ("dysontogenetic") neoplasms such as Wilm's tumor and hepatoblastoma. They also argued that the presence of blastematous features in addition to myogenic differentiation separates PPB from embryonal rhabdomyosarcoma.

More recently Priest et al. added 39 additional patients and summarized their experience with 50 patients, including many of the previously published examples (Table 19-1). In addition to confirming observations made in 1988, this expanded series highlights developments that have occurred in the intervening decade. Patients were divided into three groups based on gross morphology of the tumor: *type I* (purely cystic), *type II* (solid and cystic) and *type III* (purely solid). Patients with cystic tumors (type I) were younger and enjoyed the best overall prognosis. Thirteen patients were characterized as having "familial" disease, meaning that they either had associated dysplastic or neoplastic conditions themselves or had family members with related conditions (e.g. PPB, medulloblastoma, embryonal rhabdomyosarcoma, synovial sarcoma, congenital adenomatoid malformations). Lung was involved in the majority of patients and was accompanied by parietal pleural and/or mediastinal disease in some patients. Isolated pleural (1) or pleural and mediastinal (2) disease without lung involvement was limited to 3 patients, all with purely solid (type III) tumors. Surgical procedures were characterized as "major", gross total removal, or enbloc resections in 31 patients, including 11 solid tumors. Eleven patients had only partial resection and one had biopsy only.

Tumors ranged in size from 2 to 28 cms in size. Type I tumors were characterized by multiloculated cysts separated by thin fibrous septa which were frequently lined by non-neoplastic respiratory epithelium. Small, round to spindle shaped tumor wells were often distributed in a condensed fashion beneath the non-neoplastic epithelium in a manner analogous to the cambium layer of sarcoma botryoids. Solid zones in type II and type II PPB were composed of variable proportions of blastematous and sarcomatous stroma. Blastematous foci were composed of primitive small cells which contrasted with less cellular sarcomatous zones composed of spindle cells resembling malignant fibrous histiocytomas or fibrosarcoma. Focal skeletal muscle differentiation was identified in most cases. Cartilaginous differentiation in the form of a focal chondroid matrix or well formed islands of hyaline cartilage were identified in over half (60%) type I and type II tumors, but was seen in only two (of 19) purely solid tumors.

The main ***differential diagnosis*** includes the more classical "adult type" of *pulmonary blastoma* and *other forms of sarcoma.* "Adult" pulmonary blastomas differ not only in terms of the clinical context but also by virtue of a neoplastic epithelial component (see Table 19-2). There is little doubt that at least some examples of purely cystic (type I) PPB could as easily be considered variants of rhabdomyosarcoma. Most examples, however, differ in that the rhabdomyosarcomatous elements are accompanied by a histologically distinctive blastematous component. Indeed it is the presence of the blastematous component that separates PPB from other forms of sarcoma with which these tumors might be confused, including monophasic synovial sarcoma, malignant peripheral nerve sheath tumors, malignant fibrous histiocytoma, and fibrosarcoma.

TABLE 19-1: SUMMARY OF 50 PATIENTS WITH PLEUROPULMONARY BLASTOMA
Priest J. et al. *Cancer* 1997; 80:147-61

	ALL PATIENTS	TYPE I	TYPE II	TYPE III	P value
N	50	7 (14%)	24 (48%)	19 (38%)	
Median age (range)	38 mos (0-147 mos)	10 mos (0-28 mos)	34 mos (15-64 mos)	44 mos (31-147 mos)	<0.001
Males:Females	24:26	3:4	9:15	12:7	0.2
Symptoms					
resp distress	21 (42%)				
fever	16 (32%)				
chest/abd pain	13 (26%)				
cough	13 (26%)				
anorexia	6 (12%)				
malaise	5 (10%)				
Primary site (L; P; M)	Rt=32 Lt=18 (47; 19; 11)	Rt=3 Lt=4 (7; 0; 0)	Rt=19 Lt=5 (24; 9; 5)	Rt=10 Lt=9 (16; 10; 6)	0.09
Familial	13 (26%)	2 (29%)	8 (33%)	3 (16%)	0.7
Median followup (range)	26 mos (0-199 mos)	24 mos (4-199 mos)	34 mos (8-130 mos)	22 mos (0-185 mos)	0.9
Adjuvant therapy					
chemotherapy	40/45 (89%)	3/6 (50%)	20/21 (95%)	17/18 (94%)	0.2
radiation	14/46 (30%)	0/6	4/23 (17%)	10/17 (59%)	0.004
Recurrence/mets	25/50 (50%)	1/7 (14%)	13/24 (54%)	11/19 (58%)	
ipsilateral	19	1	11	7	
contralateral	2		2		
bone	6		3	3	
brain/cord	11		5	6	
Outcome					
NED	24 (48%)	6 (86%)	12 (50%)	6 (36%)	
AWD	2 (4%)		1 (4%)	1 (5%)	
DOD	22 (44%)	1 (14%)	11 (46%)	10 (53%)	
(mean survival)	(18 mos)	(5 mos)	(22 mos)	(15 mos)	

Abbreviations: mos: months; resp: respiratory; abd: abdominal; Rt: right; Lt: left; L: lung; P: parietal pleura; M: mediastinum; NED: no evidence of disease; AWD: alive with disease; DOD: dead of disease

TABLE 19-2: COMPARISON OF WELL-DIFFERENTIATED FETAL ADENOCARCINOMA (WDFA), CLASSICAL "ADULT" BIPHASIC PULMONARY BLASTOMA, AND PLEUROPULMONARY BLASTOMA (PPB)

Modified from Colby et al. Atlas of Tumor Pathology (Third Series, Fascicle 13). *Tumors of the Lower Respiratory Tract.* Armed Forces Institute of Pathology. Washington, DC 1994, p. 396

	WDFA	Biphasic Blastoma	PPB
CLINICAL			
patients < 10 years of age	0	8%	91%
History of cigarette smoking	Common	Common	No
Location	Lung	Lung	Lung, pleura, mediastinum
Average size	4.5 cms	10.1 cms	—
Asymptomatic	Often	Uncommon (~ 20%)	Rare
Prognosis	Good	Poor	Poor
PATHOLOGIC			
Malignant epithelium/ Malignant stroma	Present/Absent	Present/Present	Absent/Present
Morules present	86%	43%	0
Neuroendocrine differentiation	Frequent	Frequent	Never

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Case #20

Clinical History - Acc. # 29166

A 47-year-old woman, never smoker, presented for evaluation of an abnormal chest x-ray. About 6 weeks prior to admission she noted a "catch" in her right lateral chest wall. A chest radiograph showed a 6 x 8 cms mass in the right costophrenic angle and a 1.2-cm noncalcified density in the left posterior costophrenic angle. Physical examination was unremarkable. Past medical history included a previous hysterectomy and bilateral salpingo-oophorectomy 12 years prior to admission. She underwent wedge excision of left lower lobe and right middle lobe nodules.

Diagnosis: *Metastatic Endometrial Stromal Sarcoma*

Follow-up: Review of her previous hysterectomy specimen demonstrated a low grade endometrial stromal sarcoma forming a 6 x 2 x 1.5 cms polypoid mass arising in the fundus. She returned nearly 4 years after resection of her pulmonary metastases and underwent resection of multiple additional lung and pleural nodules. She was alive 20 months after her second thoracotomy, but the status of her disease was unknown.

Discussion:

Low-grade endometrial stromal sarcoma (ESS) is a rare low-grade neoplasm, accounting for fewer than 1% of uterine malignancies. ESS are infiltrative tumors composed of cytologically bland cells resembling stromal cells of normal proliferative endometrium. Histological variation may include hyalinization, necrosis, cysts, decidualization, epithelial differentiation with a glandular or sex cord-like pattern, and smooth muscle differentiation. ESS has a favorable prognosis with 5 and 10-year survival rates of nearly 100%. Recurrence tends to be limited to the pelvis. Rare patients develop distant metastases, the most commonly affected site being lung. Pulmonary metastases can occur after long tumor-free intervals and in this circumstance may pose a diagnostic challenge.

In a recent review of the Mayo Clinic and Anatomic Pathology consultation files, lung specimens from 15 patients with metastatic ESS were identified. Patients were 31.0 to 77.0 years of age (mean 50.5 years) at time of lung biopsy. Uterine ESS had been diagnosed 2.5 to 20.0 years (mean 9.0 years) prior to lung biopsy in 11 patients. Previously resected uterine ESS were called smooth muscle tumors 3.0 to 10.0 years (mean 13.6 yrs) prior to lung biopsy in 3 additional patients. Thirteen patients presented for evaluation of new pulmonary nodules which were asymptomatic in 7. Lung nodules were multiple in 10 and solitary in 4, their largest size ranging from 1 to 8 cms (mean 2.9 cms). Follow-up was available in 11 patients. One patient died of disease; ten were alive, 6 without disease. Diagnostic considerations in 11 consultation cases included ESS (5), sclerosing hemangioma

(2), carcinoid (2), lymphangioleiomyomatosis (LAM) (1), endometriosis (1), hemangiopericytoma (1) and lymphoma (1).

The histologic features of metastatic ESS tend to mirror the features associated with uterine primaries. Most present as well-circumscribed solid tumors composed of short spindle cells with prominent associated thin walled vessels, resembling a "hemangiopericytoma-like" pattern. The nuclei are round to oval with little atypia. Mitotic figures are rare. Epithelial differentiation characterized by sex-cord like tubules can occur, and was seen in two of our cases. Smooth muscle differentiation can also occur and was a focal finding in four of our cases. Occasional cases may be predominantly cystic. Indeed an example of metastatic ESS was included in Dr. Mark's study of what he then termed cystic mesenchymal hamartomas. Less commonly metastatic ESS demonstrates a lymphangitic growth pattern. Immunohistochemical studies may be helpful in that most cases are positive not only for vimentin but also estrogen and progesterone receptor proteins. Immunoreactivity for smooth muscle actin and desmin occur in some patients and tends to be most pronounced in areas of sex-cord like and smooth muscle differentiation. Stains for keratin, neuroendocrine markers, and HMB45 are consistently negative.

It is important to suspect metastases from unlikely sources when confronted with multiple, or even solitary, lung nodules of unusual histology. *With rare exception, multiple tumors that are difficult to classify turn out to represent metastases.* This applies particularly to low grade tumors not usually associated with a potential for metastasizing (*e.g.* cutaneous fibrous histiocytoma, cutaneous dermatofibrosarcoma protuberans, low grade leiomyosarcoma, salivary gland tumors including "benign" pleomorphic adenoma, paragangliomas, giant cell tumor of bone, and "benign" thymoma). In many of these circumstances, either the history or an undiscovered primary site may be unknown to the surgeon or others caring for the patient at the time the lung disease is being investigated.

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Case 1: Sclerosing mediastinitis

(a) Low magnification photomicrograph demonstrating peribronchiolar fibrosis. The mucosa of a large cartilaginous airway is relatively preserved. Outside the bronchial cartilage there is densely sclerotic stroma with a patchy mononuclear inflammatory infiltrate. (b) High magnification view of coarse collagen bundles associated with a scant infiltrate of lymphocytes and plasma cells. (c) Low magnification photomicrograph demonstrating the "invasive" relationship of stromal sclerosis to uninvolved connective tissue at the lung hilum.

Case 2: Hamartoma

(a) Low magnification photomicrograph showing a hamartoma with areas of papillary growth. The hamartoma comprises a mixture of cartilage and fibromyxoid tissue. (b) Higher magnification photomicrograph demonstrating paucicellular fibromyxoid tissue adjacent to hyaline cartilage. (c) High magnification view demonstrating fibromyxoid stroma typical of pulmonary hamartomas. The epithelial element represents non-neoplastic incorporated respiratory epithelial cells.

Case 3: Sclerosing Hemangioma

(a) Low magnification photomicrograph demonstrating a relatively well-circumscribed neoplasm with a heterogeneous appearance. The periphery shows blood-filled spaces resembling that seen in vascular neoplasms. (b) Higher magnification view demonstrating an area of sclerosis with associated cytologically bland cuboidal cells. The spaces contain finely vacuolated lipid-laden histiocytes. (c) High magnification photomicrograph demonstrating the pale cuboidal cells of sclerosing hemangioma.

Case 4: Inflammatory Myofibroblastic Tumor (Plasma Cell Granuloma)

(a) Intermediate magnification photomicrograph demonstrating cytologically bland spindle cells arranged in ill-defined interlacing fascicles. The spindle cells, representing the neoplastic population, are intimately associated with an infiltrate of mononuclear inflammatory cells. (b) Higher magnification photomicrograph demonstrating an area in which spindle cells are partially obscured by non-neoplastic plasma cells. (c) High magnification photomicrograph demonstrating the intimate relationship between spindled myofibroblastic cells and plasma cells.

Case 5: Epithelioid Hemangioendothelioma mimicking Mesothelioma

(a) Low magnification photomicrograph showing dramatically thickened visceral pleura. The thickened visceral pleura appear mainly fibrotic. The population of neoplastic cells is difficult to visualize at this magnification. At the interface between thickened pleura and underlying alveolated lung parenchyma are tuffs of neoplastic cells resembling alveolar histiocytes. (b) High magnification photomicrograph demonstrating cytologically bland epithelioid cells randomly distributed in the fibrotically thickened visceral pleura. (c) High magnification photomicrograph demonstrating histiocyte-like neoplastic cells within alveolar

spaces. The neoplastic cells have eccentrically located nuclei and abundant eosinophilic cytoplasm with focally prominent coarse cytoplasmic vacuoles.

Case 6: Atypical Carcinoid Tumor

(a) Intermediate magnification photomicrograph demonstrating an organoid growth pattern characteristic of carcinoid tumors. (b) High magnification photomicrograph demonstrates mildly atypical neoplastic cells with easily identifiable mitotic figures. (c) Focally the tumor demonstrates necrosis in the central areas of neoplastic nests. This pattern of necrosis is characteristic of atypical carcinoid tumors.

Case 7: Bronchioloalveolar Carcinoma

(a, b) Low and intermediate magnification photomicrographs demonstrating classical bronchioloalveolar growth pattern. (c) High magnification view showing relatively bland columnar cells arranged in a "lepidic" growth pattern on intact alveolar septa.

Case 8: Large Cell Carcinoma

(a) Low magnification photomicrograph demonstrating a high-grade carcinoma with a relatively non-descript growth pattern. To some, this may appear as a "neuroendocrine" architecture. (b) High magnification photomicrograph demonstrating neoplastic cells with coarse chromatin, small but conspicuous nucleoli, and relatively scant cytoplasm. (c) High magnification photomicrograph from another portion of the tumor in which pleomorphic giant cells are easily identified.

Case 9: Adenocarcinoma arising in Usual Interstitial Pneumonia

(a) Low magnification photomicrograph showing atypical epithelium lining airspaces in an area of dense subpleural scarring. (b) High magnification photomicrograph showing relatively bland columnar mucinous cells arranged in an acinar growth pattern within an area of fibrosis. Although the cytologic features are relatively bland, this represents an area of adenocarcinoma. (c) Intermediate magnification photomicrograph demonstrating an area of acinar adenocarcinoma.

Case 10: Sarcomatoid (Pleomorphic) Carcinoma

(a) High magnification photomicrograph demonstrating neoplastic spindle cells arranged in a pattern resembling sarcoma. (b) Low magnification photomicrograph demonstrating spindle cell carcinoma with a myxoid stroma occluding a vascular lumen. (c) High magnification photomicrograph demonstrating neoplastic giant cells.

Case 11: Pulmonary Blastoma

(a) Low magnification photomicrograph demonstrating biphasic tumor growing as an exophytic endobronchial lesion. (b) High magnification photomicrograph of the sarcomatoid component showing relatively undifferentiated blunt spindle cells with abundant mitoses and apoptoses. (c) Photomicrograph demonstrating glandular

component with an acinar architecture resembling that seen in endometrioid adenocarcinomas.

Case 12: Respiratory Papillomatosis involving the lung

(a, b) Low and intermediate magnification photomicrographs demonstrating replacement of distal bronchiolar epithelium by bland squamous cells. The bland squamous epithelium extends into peribronchiolar airspaces and involves intact alveolar septa without distorting lung architecture. (c) Periphery of "tumor nodule" again demonstrating intimate relationship between bland squamous epithelium and columnar respiratory cells. The squamous epithelium grows as airspace buds without evidence of invasion.

Case 13: Metastatic Angiosarcoma

(a) Low magnification photomicrograph demonstrating angiosarcoma growing around a large pulmonary vein. (b, c) High magnification photomicrographs demonstrating histologic features typical of angiosarcoma with complex anastomosing vascular channels.

Case 14: Solitary Fibrous Tumor

(a) Low magnification photomicrograph showing a relatively cellular tumor with a prominent vascular stroma. (b, c) High magnification photomicrograph demonstrating cytologically bland spindle cells arranged in a collagenous stroma in patterns that resemble those seen in other benign soft tissue tumors, such as neurilemmoma.

Case 15: Wegener's Granulomatosis

(a) Low magnification photomicrograph demonstrating an area of necrosis associated with a granulomatous inflammatory reaction that includes prominent multinucleated giant cells. (b) High magnification photomicrograph demonstrating a granulomatous microabscess. This lesion is typical of Wegener's granulomatosis. (c) Necrotizing vasculitis involving a small pulmonary artery.

Case 16: Lymphomatoid Granulomatosis

(a) Low magnification photomicrograph demonstrating a dense lymphocytic infiltrate surrounding an area of central necrosis (lower). (b) Low magnification photomicrograph demonstrating prominent infiltration into otherwise intact vessel walls. (c) High magnification photomicrograph demonstrating a polymorphic lymphoid infiltrate that includes atypical large cells with vesicular chromatin and prominent nucleoli.

Case 17: Extranodal Marginal Zone B-Cell Lymphoma of MALT type

(a) Low magnification photomicrograph demonstrating striking lymphangitic infiltrate distributed along visceral pleura, interlobular septa, and bronchovascular bundles. (b) Intermediate magnification photomicrograph showing relatively monomorphic infiltrate of small lymphocytes. (c) High magnification

photomicrograph demonstrating small lymphocytes with mildly irregular nuclear contours. There is a minor background population of larger cells with vesicular chromatin and prominent nucleoli.

Case 18: Lymphangioleiomyomatosis

(a) Low magnification photomicrograph showing cystic spaces. (b) High magnification photomicrograph demonstrating a portion of one of the cysts demonstrated in "a". The alveolar septum is thickened by an infiltrate of spindled cells with cytologic characteristics of smooth muscle. (c) Intermediate magnification photomicrograph again demonstrating smooth muscle cells with associated hemosiderin pigment, a common finding in lymphangioleiomyomatosis.

Case 19: Pleural Pulmonary Blastoma

(a) Low magnification photomicrograph demonstrating variably cellular connective tissue septa in a complex multiloculated cystic tumor. (b) Higher magnification photomicrograph demonstrating a portion of one of the connective tissue septa in which neoplastic cells are arranged beneath non-neoplastic respiratory epithelium. The growth pattern resembles that seen in botryoid variants of rhabdomyosarcoma. (c) High magnification photomicrograph demonstrating rhabdomyoblasts with associated primitive spindle cells.

Case 20: Metastatic Low-Grade Endometrial Stromal Sarcoma

(a) Low magnification photomicrograph demonstrating a well circumscribed encapsulated tumor. (b, c) Intermediate and high magnification photomicrographs demonstrating blunt spindle cells typical of low-grade endometrial stromal sarcoma. The cells are arranged in sheets with a vascular stromal background.

California Tumor Tissue Registry

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CALIFORNIA TUMOR TISSUE REGISTRY

is proud to announce our upcoming 110th Semi-Annual Cancer Seminar:

"Intrathoracic Neoplasms"

Jeffrey Myers, M.D

Mayo Clinic, Rochester, Minnesota

Sunday, June 3, 2001
8:30 a.m. - 4:30 p.m.
Westin South Coast Plaza
Costa Mesa, California

Dr. Jeffrey Myers, M.D., Chair, Division of Anatomic Pathology, Mayo Clinic, Rochester Minnesota, is one of the most respected pulmonary pathologists in the United States. Following graduation from Washington University School of Medicine, he took pathology residency training at Washington University School of Medicine, Barnes and Affiliated Hospitals, where he was also the American Cancer Society Regular Clinical Fellow. He did a surgical pathology fellowship at the University of Alabama, Birmingham, Alabama, and a pulmonary pathology fellowship with Anna-Louise Katzenstein at the University of Alabama. He is the recipient of numerous awards, and was voted the best basic science professor at the University of Alabama, Birmingham School of Medicine. He is Professor of Pathology in the Mayo Medical School, and has served as the short course coordinator of the US-CAP. He is on the editorial boards of several medical journals, and is widely sought out as a visiting professor and lecturer. Dr Myers is widely published and is the author of 10 book chapters. His lecture on "Intrathoracic Tumors" will be a lecture not to be missed.

Educational Contents and Media:

1. Glass slides representative of twenty tumors or tumor-like conditions of the lung and mediastinum.
2. Correlating clinical histories
3. Six hour lecture, incorporating projected photographs of cases and other illustrative materials.
4. Comprehensive printed color syllabus, including diagnosis, discussion, and appropriate references from pertinent medical literature.

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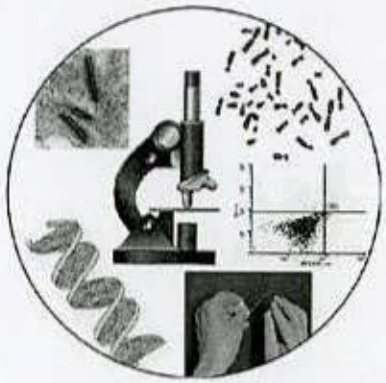
Seminar Objectives:

At the conclusion of the lecture attendees will:

- Understand the classification of conventional epithelial-derived neoplasms as well as uncommon but classic lung tumors.
- Be able to form differential diagnoses for a broad range of benign and malignant intrathoracic neoplasms.
- Have learned an appropriate diagnostic approach to tumor diagnosis which includes utilization of immunohistochemical and molecular tools.



This is a seminar that should not be missed! We'll see you in Costa Mesa!

At the conclusion of this seminar, attendees should have a differential diagnosis for a broad range of benign and malignant intrathoracic neoplasms. Areas of focus will include classification of conventional epithelial-derived neoplasms as well as uncommon but classic lung tumors. Attendees will learn an appropriate diagnostic approach that includes utilization of immunohistochemical and molecular tools.

California Tumor Tissue Registry
110th Semi-Annual Cancer Seminar

"Intrathoracic Tumors and Tumor-like Conditions"

Jeffrey L. Myers, M.D.

Resa L. Chase, M.D., Platform Chair*

7:00 a.m. - 8:30 a.m.	REGISTRATION Continental Breakfast and Exhibit Viewing
8:30 a.m. - 10:15 a.m.	LECTURE AND SLIDE PRESENTATION
10:15 a.m. - 10:30 a.m.	Refreshment Break and Exhibit Viewing
10:30 a.m. - 12:00 p.m.	LECTURE AND SLIDE PRESENTATION
12:00 p.m. - 1:30 p.m.	LUNCH BREAK
1:30 p.m. - 2:45 p.m.	LECTURE AND SLIDE PRESENTATION
2:45 p.m. - 3:00 p.m.	Refreshment Break and Exhibit Viewing
3:00 p.m. - 4:30 p.m.	LECTURE AND SLIDE PRESENTATION

* Dr. Chase is Co-Director for Education of the California Tumor Tissue Registry, and is the primary editor of the subscription study sets and syllabi for the semi-annual seminars. She has special interest in pulmonary pathology, and practices anatomic and clinical pathology at the Jerry L. Pettis Memorial Veterans Affairs Medical Center, Loma Linda, California.

Thank You Weldon!

Director Emeritus, Weldon Bullock (left), with current Executive Director Donald Chase (right). Photo taken in 1996 at the 100th semi-annual seminar, given by Dr. John Brooks. Dr. Bullock has participated in virtually every one of these 109 seminars.

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John K.C. Chan, M.D.
December 2, 2001
San Diego, California

Surgical Neuropathology
Bernd W. Scheithauer, M.D.
June 2, 2002
Costa Mesa, California

Tumors and Pre-malignant Conditions of the Gastrointestinal Tract
Robert Petras, M.D.
December 1, 2002
San Francisco, California

Advances in Surgical Pathology of Tumors
Richard L. Kempson, M.D. &
Michael R. Hendrickson, M.D.
June, 2003
Costa Mesa, California

Gynecological Neoplasms
Steven Silverberg, M.D.
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Richard M. DeMay, M.D.
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Dr. Jeffrey Myers, M.D., Chair, Division of Anatomic Pathology, Mayo Clinic, Rochester Minnesota, is one of the most respected pulmonary pathologists in the United States. Following graduation from Washington University School of Medicine, he took pathology residency training at Washington University School of Medicine, Barnes and Affiliated Hospitals, where he was also the American Cancer Society Regular Clinical Fellow. He did a surgical pathology fellowship at the University of Alabama, Birmingham, Alabama, and a pulmonary pathology fellowship with Anna-Louise Katzenstein at the University of Alabama. He is the recipient of numerous awards, and was voted the best basic science professor at the University of Alabama, Birmingham School of Medicine. He is Professor of Pathology in the Mayo Medical School, and has served as the short course coordinator of the US-CAP. He is on the editorial boards of several medical journals, and is widely sought out as a visiting professor and lecturer. Dr Myers is widely published and is the author of 10 book chapters

The California Tumor Tissue Registry is a non-profit organization dedicated to the enhancement of patient care via promotion of medical education, diagnostic consultation, and research. Serving the pathology community since 1947, it has provided its subscribers/members with semi-annual cancer slide seminars and study set materials to improve their skills and to obtain CME credit. Consultations are provided by the Registry's consultants, largely consisting of the anatomic pathology staff of Loma Linda University Medical Center. Additionally, the Registry is a repository for over 60,000 tumors, serving as an invaluable resource for cancer research. Plan to visit the ***New Web Site*** at www.cttr.org and also check out our award-winning *Case Of The Month*. Contact the Registry at voice (909) 558-4788, fax (909) 558-0188, or cttr@linkline.com.

Seminar Objectives: At the conclusion of this seminar, attendees should have a differential diagnosis for a broad range of benign and malignant intrathoracic neoplasms. Areas of focus will include classification of conventional epithelial-derived neoplasms as well as uncommon but classic lung tumors. Attendees will learn an appropriate diagnostic approach that includes utilization of immunohistochemical and molecular tools.

The California Tumor Tissue Registry
announces its 111th Semi-Annual Seminar:

"Practical Lymphoma Diagnosis: A Simplified Approach"

John K. C. Chan, M.D.

Consultant Pathologist
Queen Elizabeth Hospital
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CALIFORNIA
TUMOR TISSUE REGISTRY

110th SEMI-ANNUAL
PATHOLOGY CANCER SEMINAR

"Intrathoracic Tumors and Tumor-like Conditions"

Jeffrey L. Myers, M.D.

Professor, and Director of
Anatomic Pathology
Mayo Clinic, Rochester, Minnesota

Sunday, June 3, 2001
8:30 a.m. - 4:30 p.m.

Westin Hotel, South Coast Plaza
Costa Mesa, California

PROVIDING EXCELLENCE IN CANCER DIAGNOSIS AND EDUCATION SINCE 1947