Selected Benign & Borderline Tumors of the Lung & Pleura

Mark R. Wick, M.D.

University of Virginia Health System

Charlottesville, Virginia

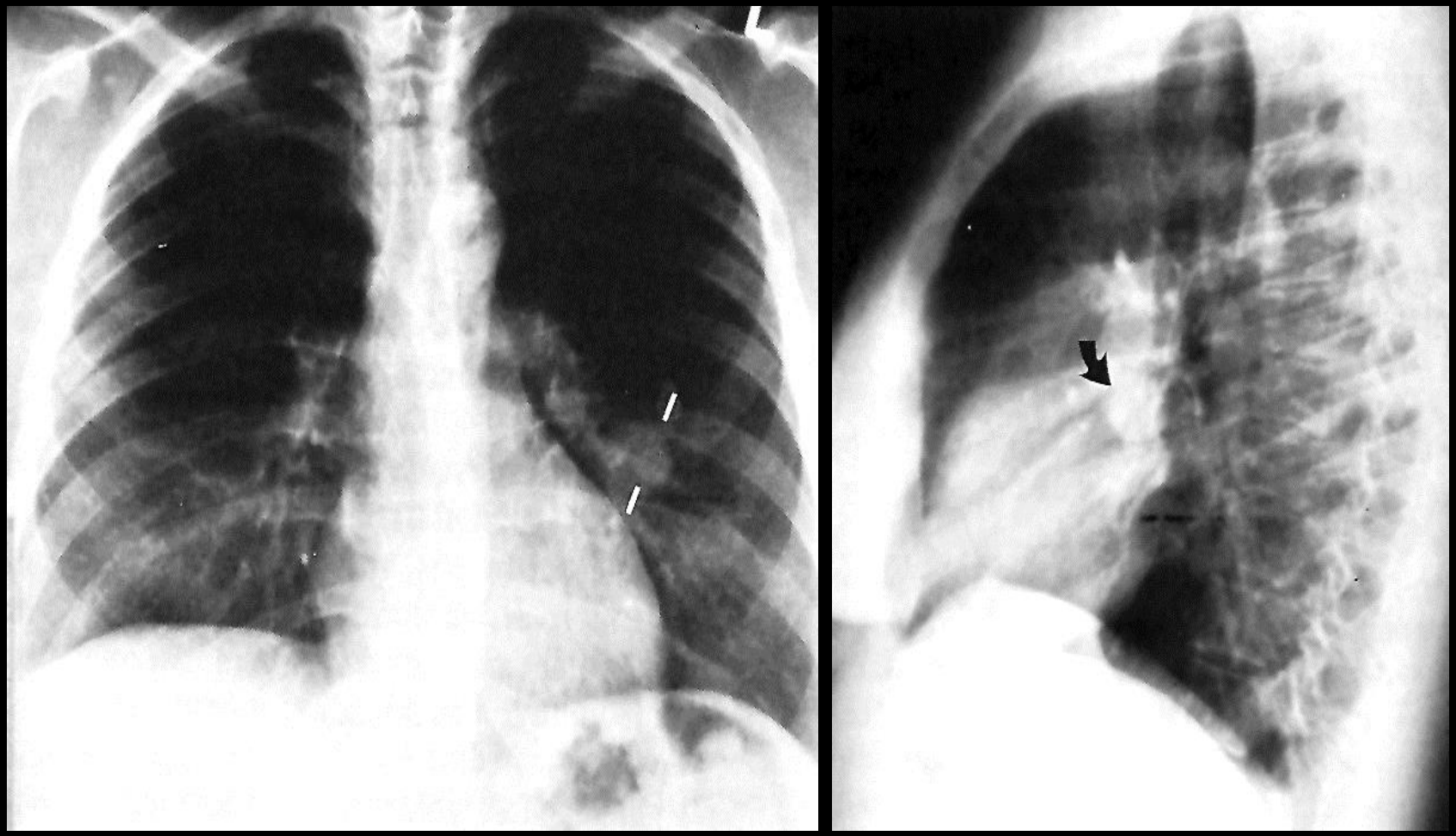
mrw9c@virginia.edu

Benign Tumors of the Lungs:
General Features

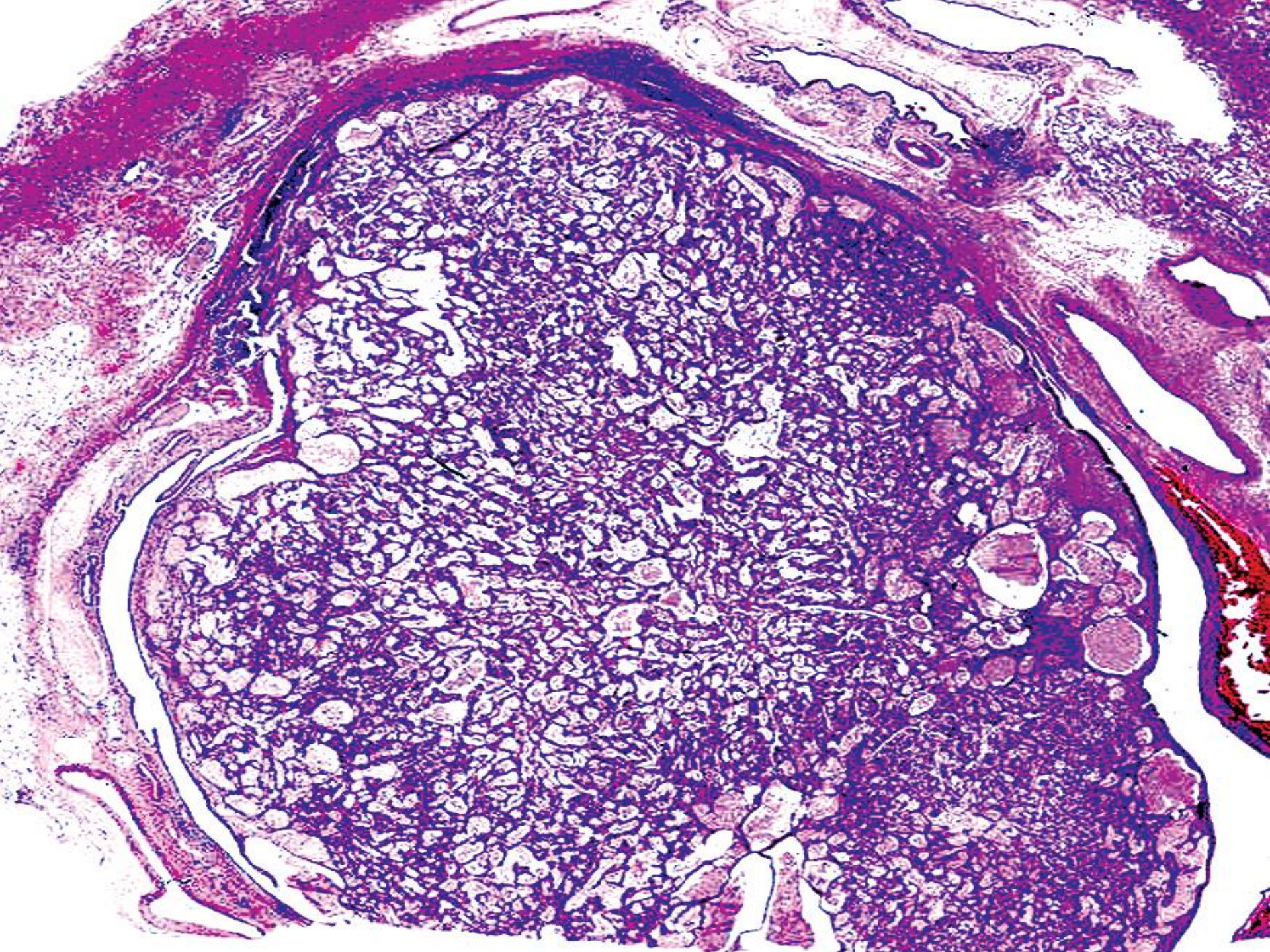
- **Symptoms & signs are not particularly distinctive; they relate to the 2 main locations of benign pulmonary tumors-- endobronchial & peripheral-intraparenchymal**
- **The first group may present with wheezing, localized emphysema, or post-obstructive pneumonia; the second is usually asymptomatic**
- **Patients of all ages are potentially affected**
- **Cytological or cutting needle-biopsy studies are usually not definitive diagnostically, because benign lesions often resemble other tumors that are low-grade malignant**

Mucous Gland Adenoma

- One of only 2 true adenomas of the tracheobronchial tree, along with pleomorphic adenoma (mixed tumor)
- Accounts for <1% of all benign neoplasms of the lungs
- Men & women equally affected, with an age range of 25 to 67 yrs.
- Asymptomatic or airway-obstructive
- CT scans better than plain films at detection

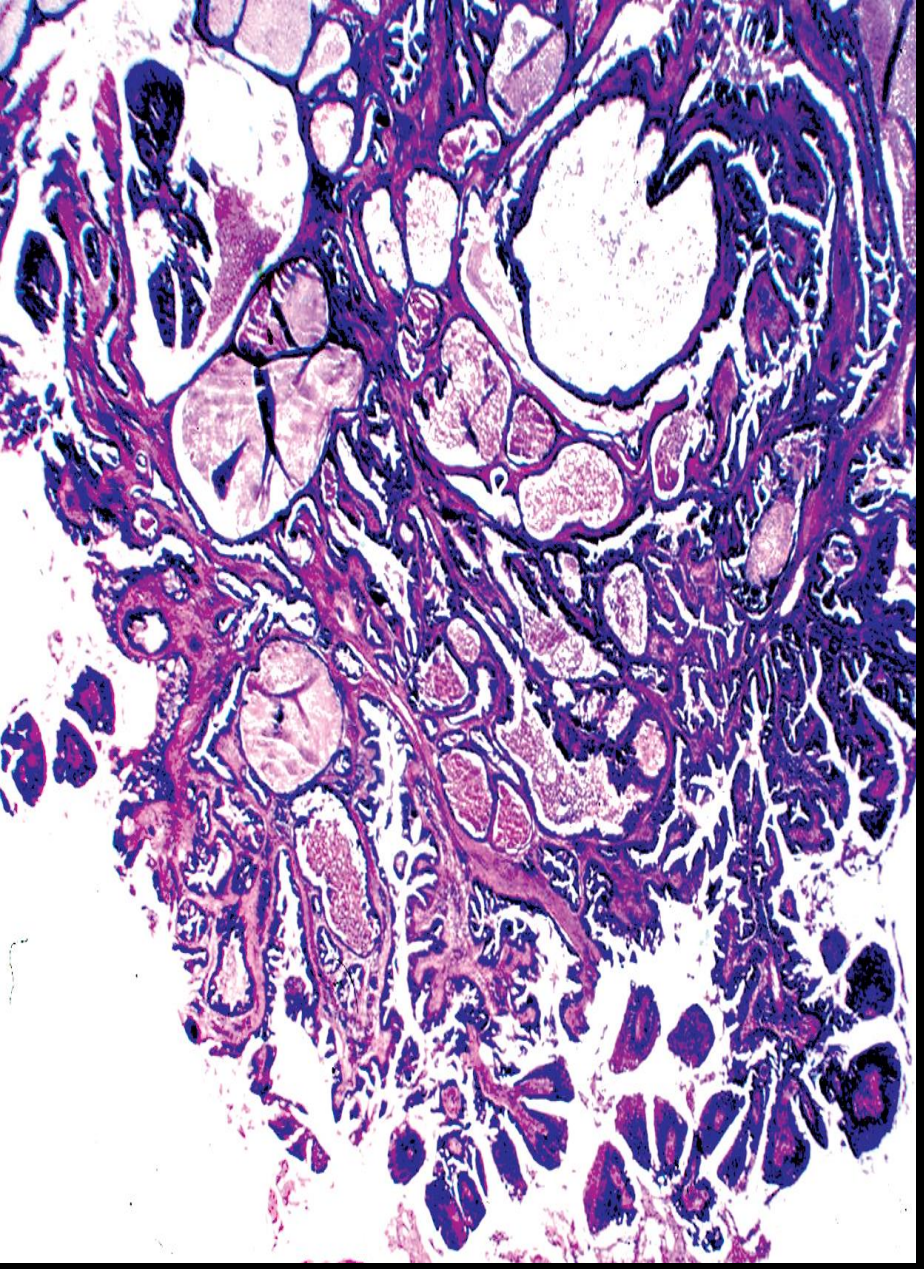


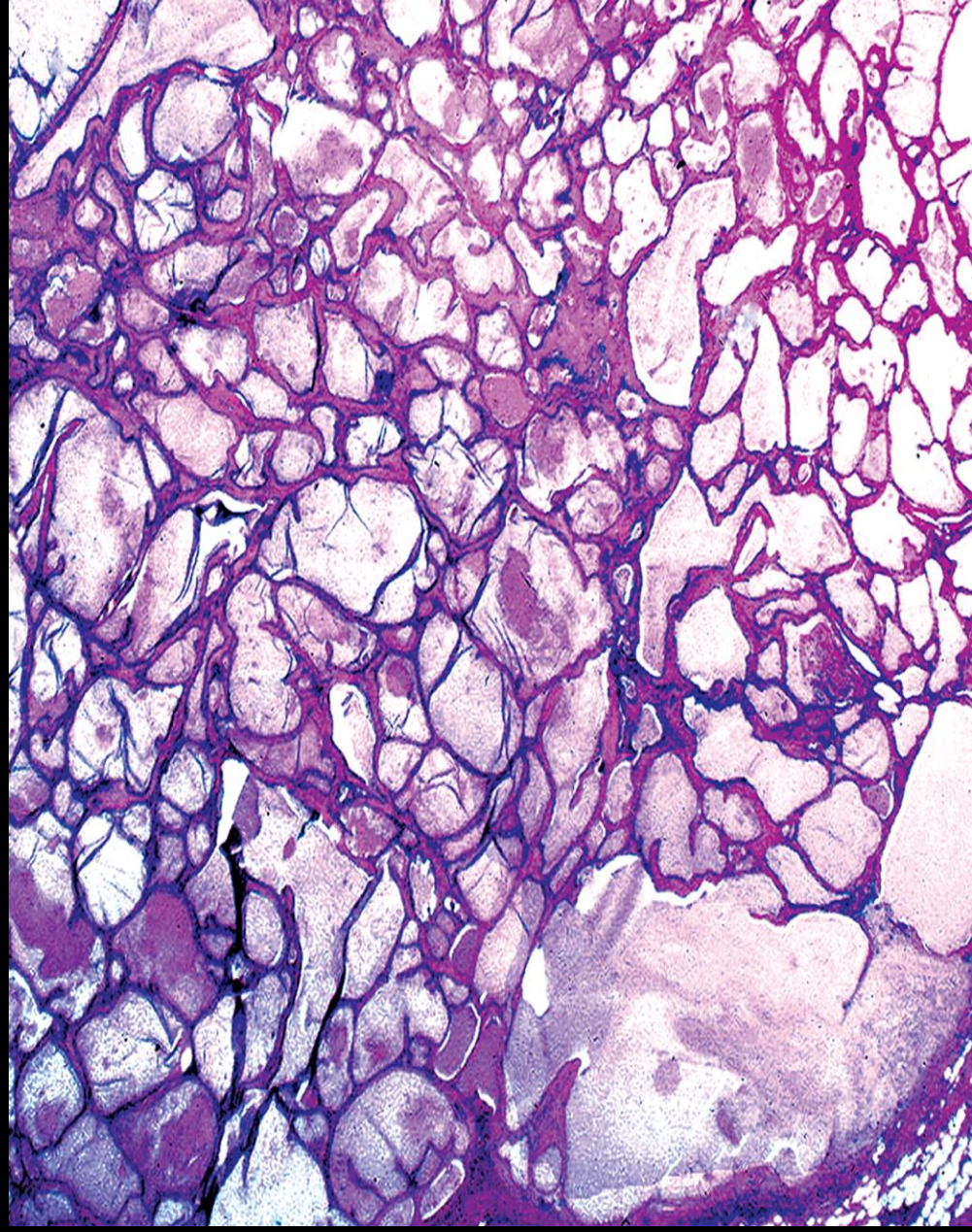
Chest Radiographs of Intrabronchial Mucous Gland Adenoma
(Courtesy of Dr. Douglas England)



Mucous Gland Adenoma

- **Two major microscopic patterns:**
  - **–Glandular-tubulocystic**
  - **–Papillocystic**

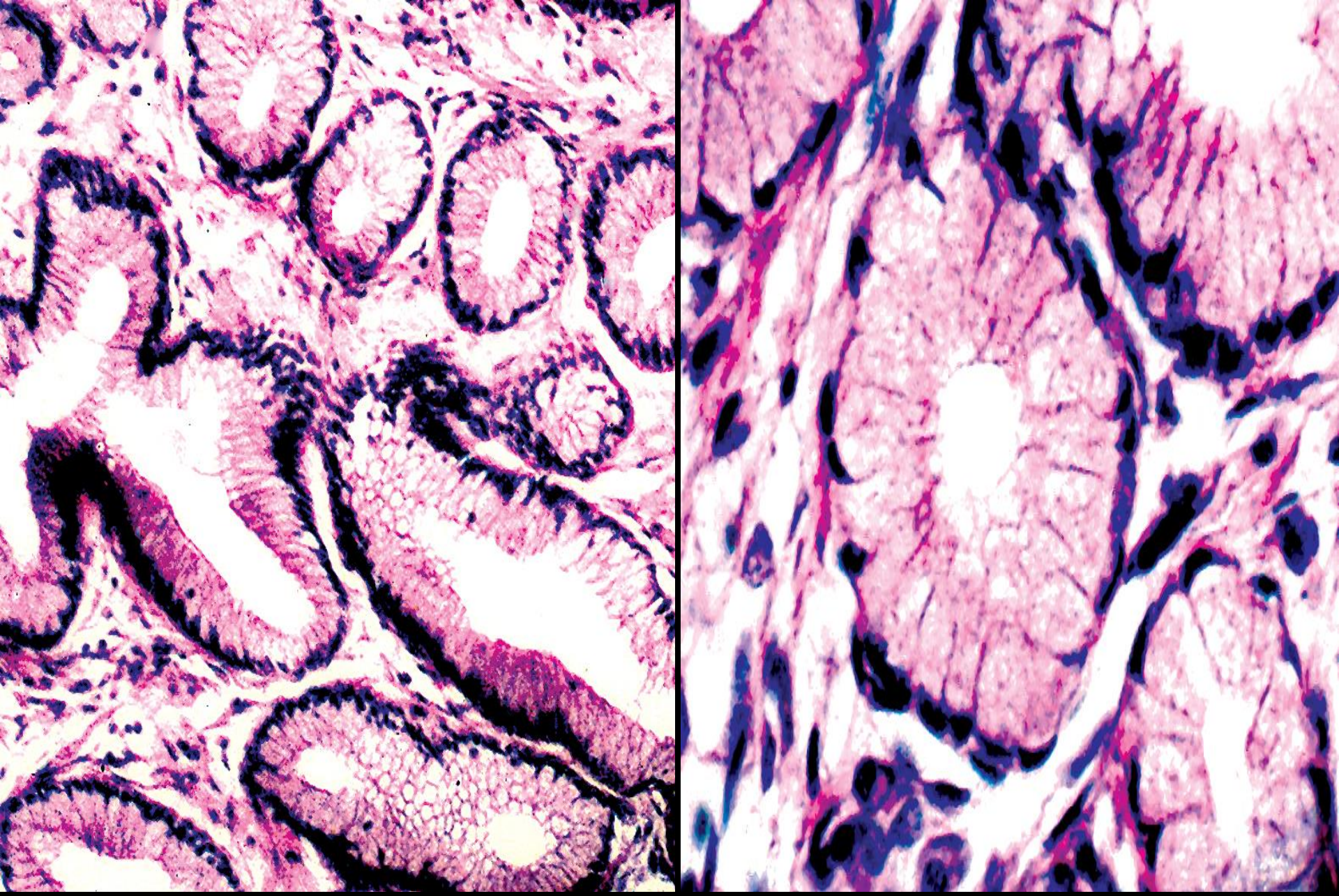




Mucous Gland Adenoma– Papillocystic & Tubulocystic Patterns

Mucous Gland Adenoma

- Often encapsulated; internal fibrous septations common as well
- Growth may permeate bronchial wall to cartilage plates but not beyond
- Internal microcystic change is a hallmark, but no atypical squamous elements are present
- Glandular cells are serous or mucinous or both
- Mitoses scarce; dystrophic calcification, cholesterol clefts, and luminal foci of squamous metaplasia may be present



Mucous Gland Adenoma– Cytological Features

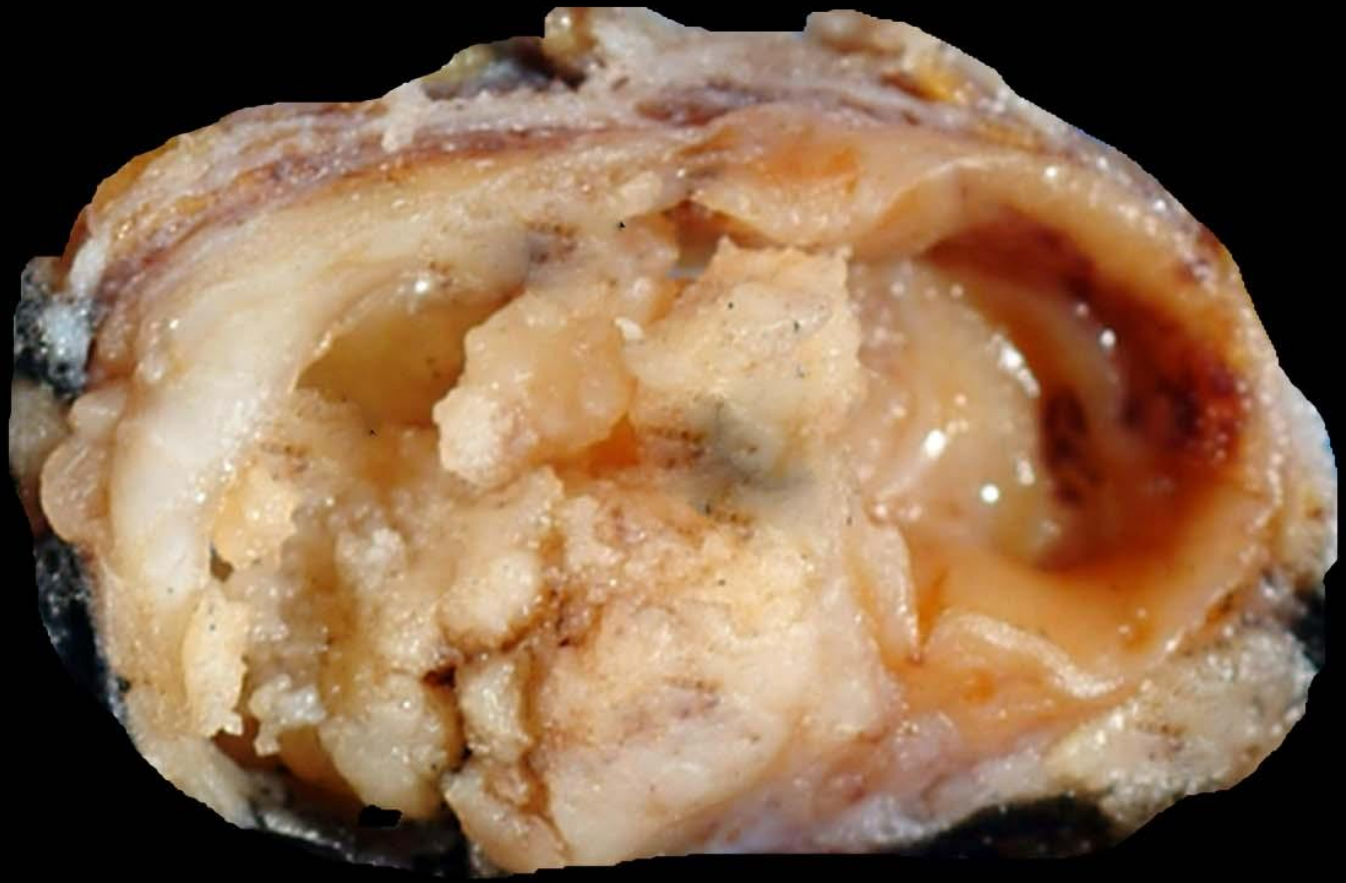
Mucous Gland Adenoma

- **Immunohistochemical studies show the presence of intratumoral myoepithelial cells that express p63, S100 protein, and alpha-isoform actin**

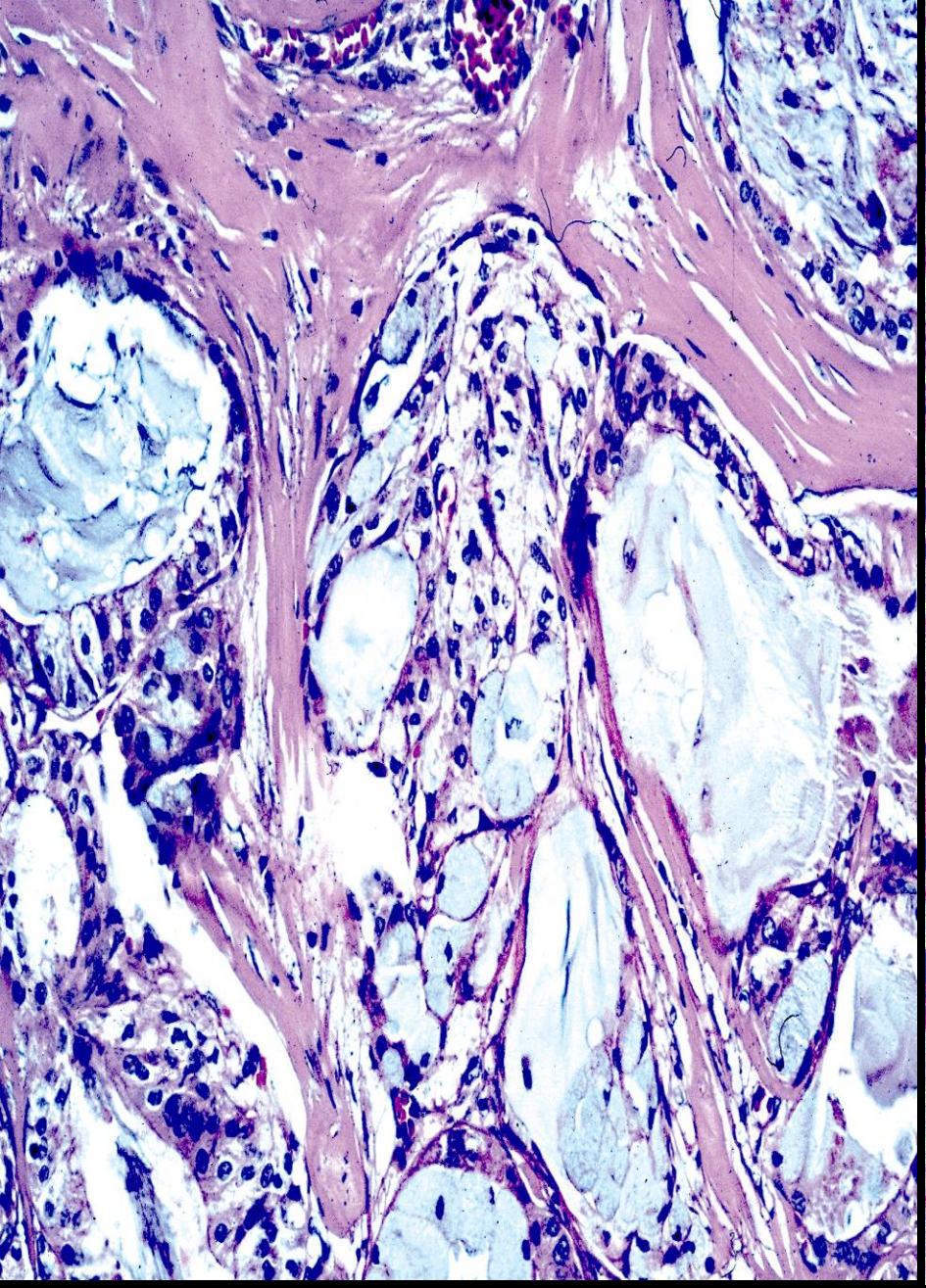
Mucous Gland Adenoma:
Differential Diagnosis

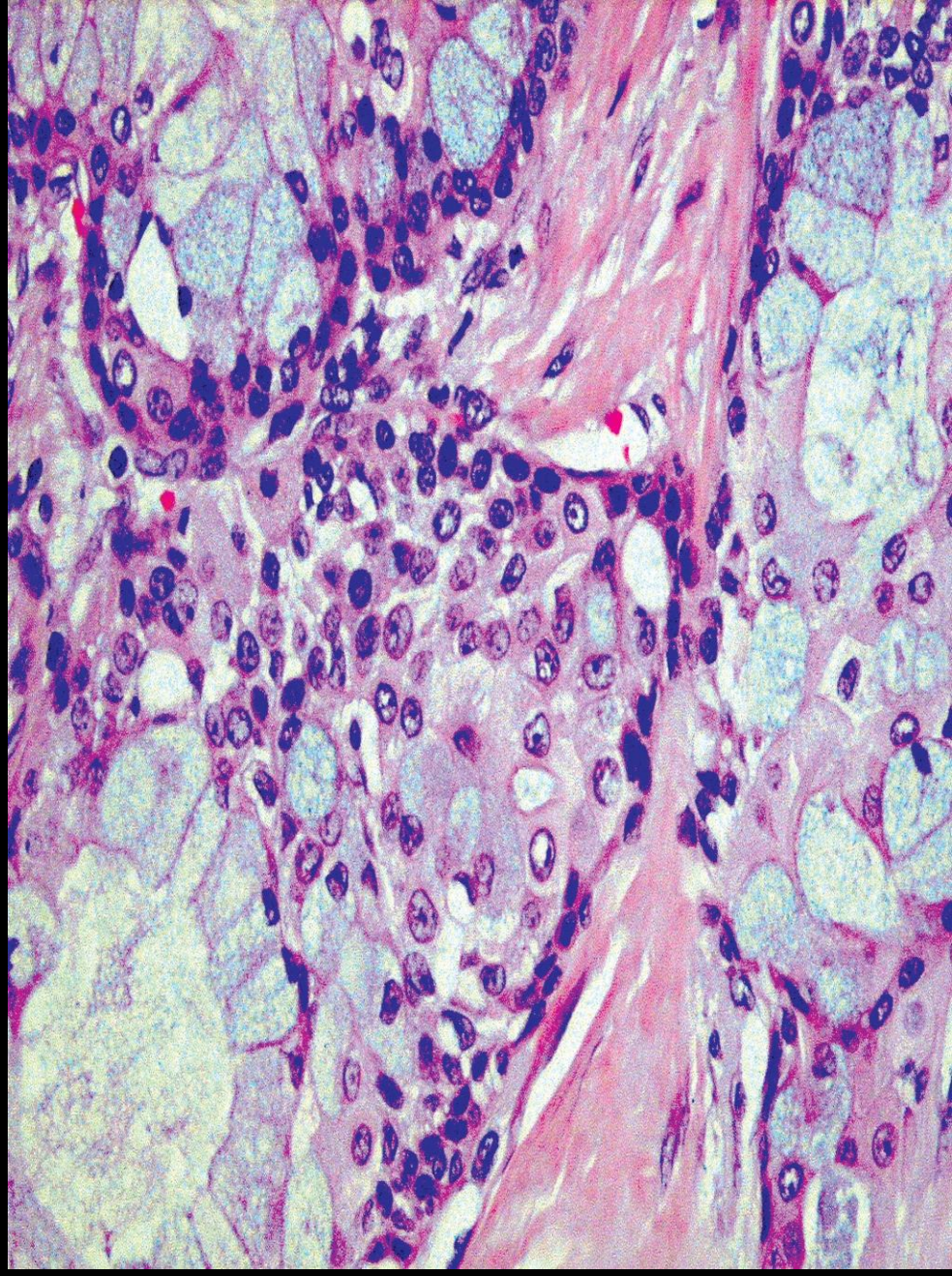
- ***Predominantly-cystic mucoepidermoid carcinoma***
- **Mixed tumor variants**
- **Pneumocytoma**
- **Well-differentiated adenocarcinoma, primary or metastatic**

A definitive diagnosis of MGA will usually require excision, and should probably not be made in small endobronchial biopsy specimens



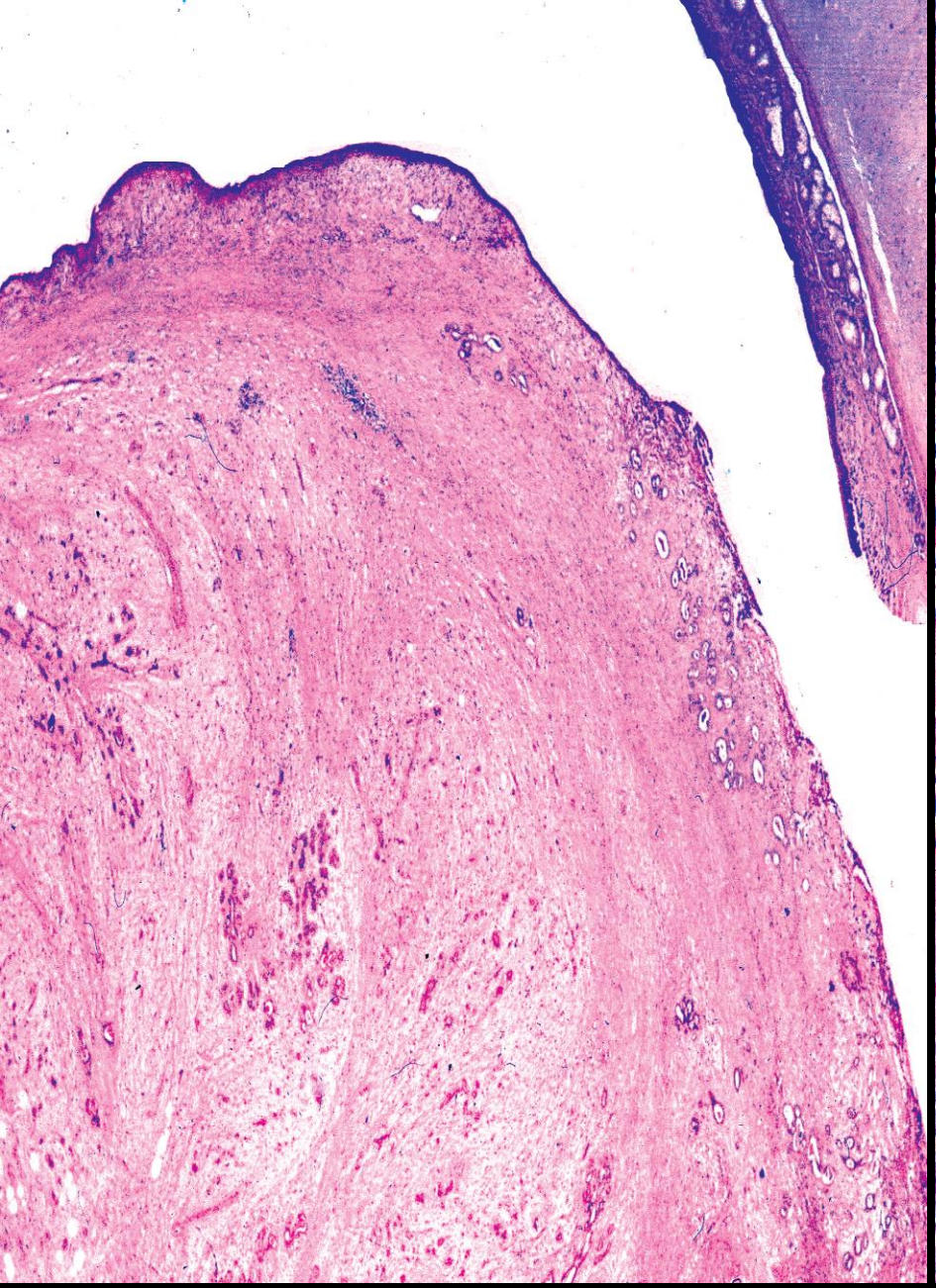
Intrabronchial Mucoepidermoid Carcinoma

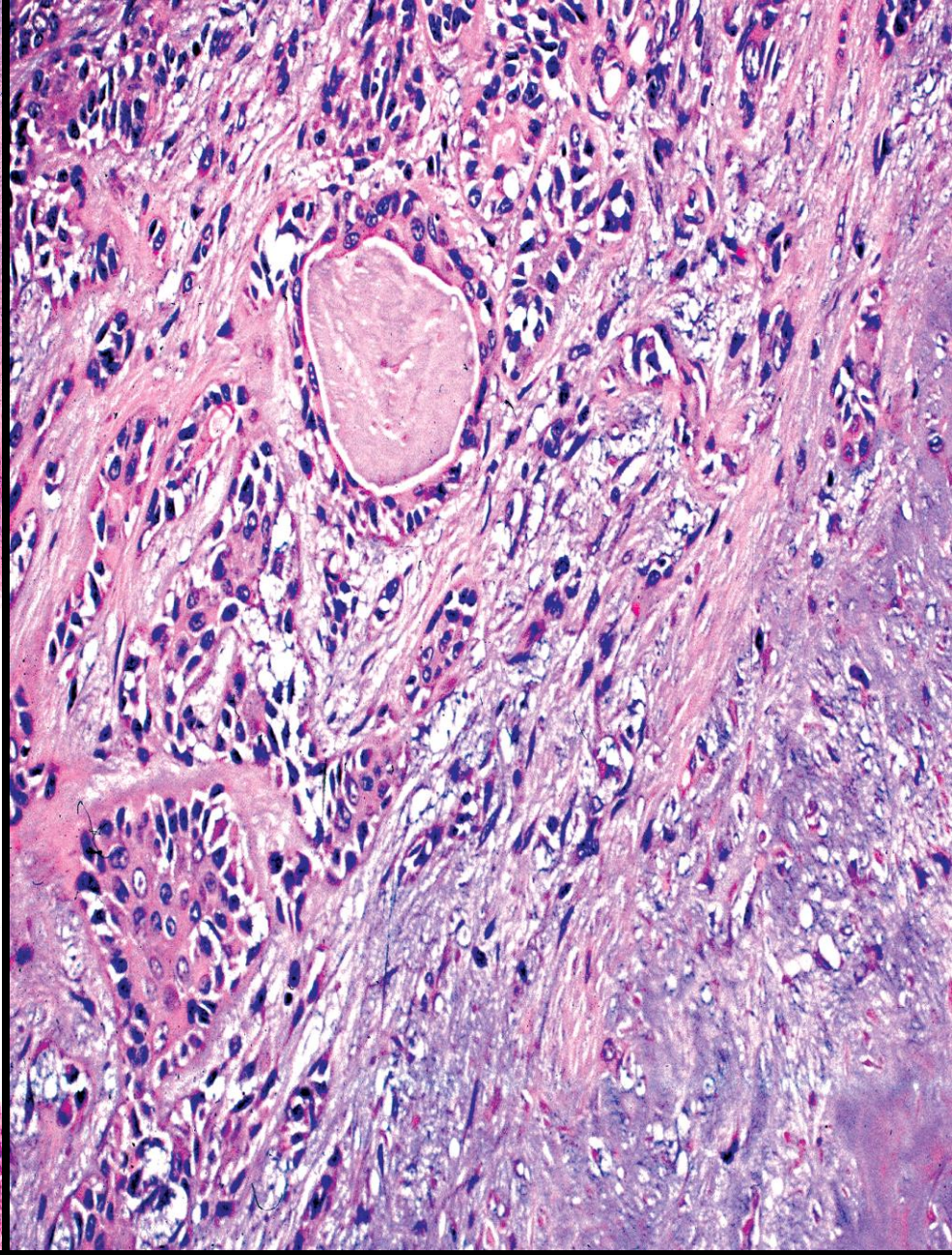




Microcystic Mucoepidermoid Carcinoma of the Lung

Bronchial Mixed Tumor (Pleomorphic Adenoma)

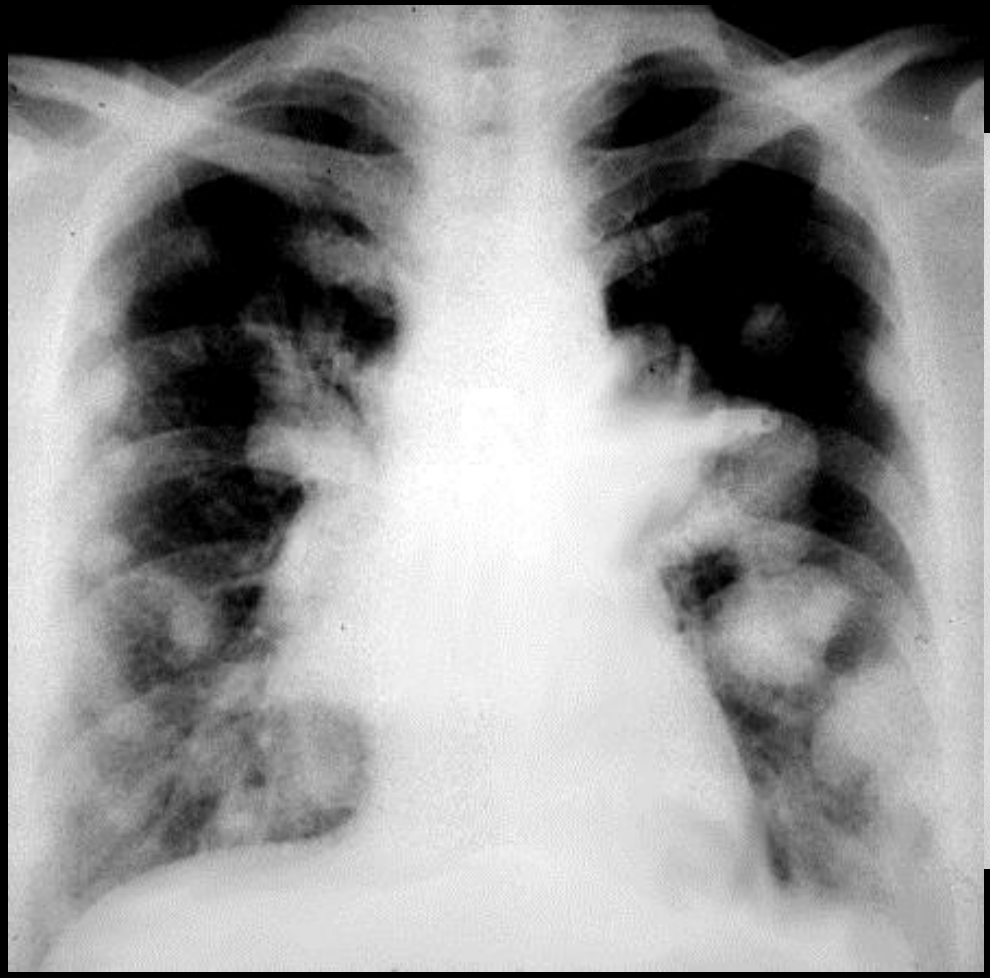


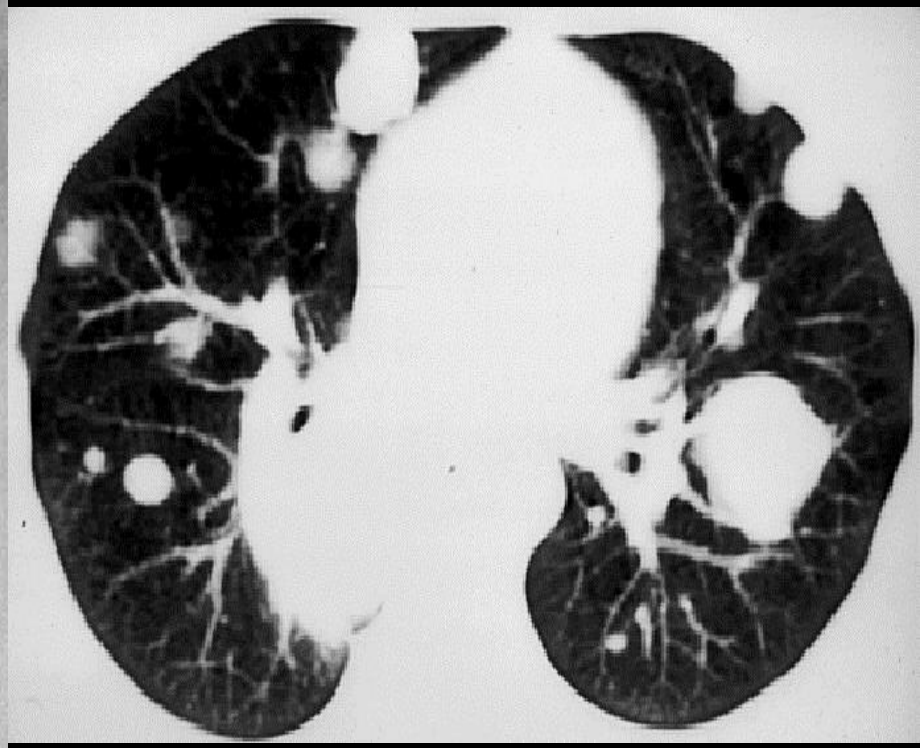


Intrabronchial Mixed Tumor (Pleomorphic Adenoma)

"Benign Metastasizing Leiomyoma" (Multifocal Leiomyomatous Hamartoma)

- Radiographically identical to tumors with a metastatic pattern
- Confined to women, most of whom have had prior hysterectomies for uterine leiomyomas
- Individual lesions vary greatly in size, and may have a "miliary" distribution

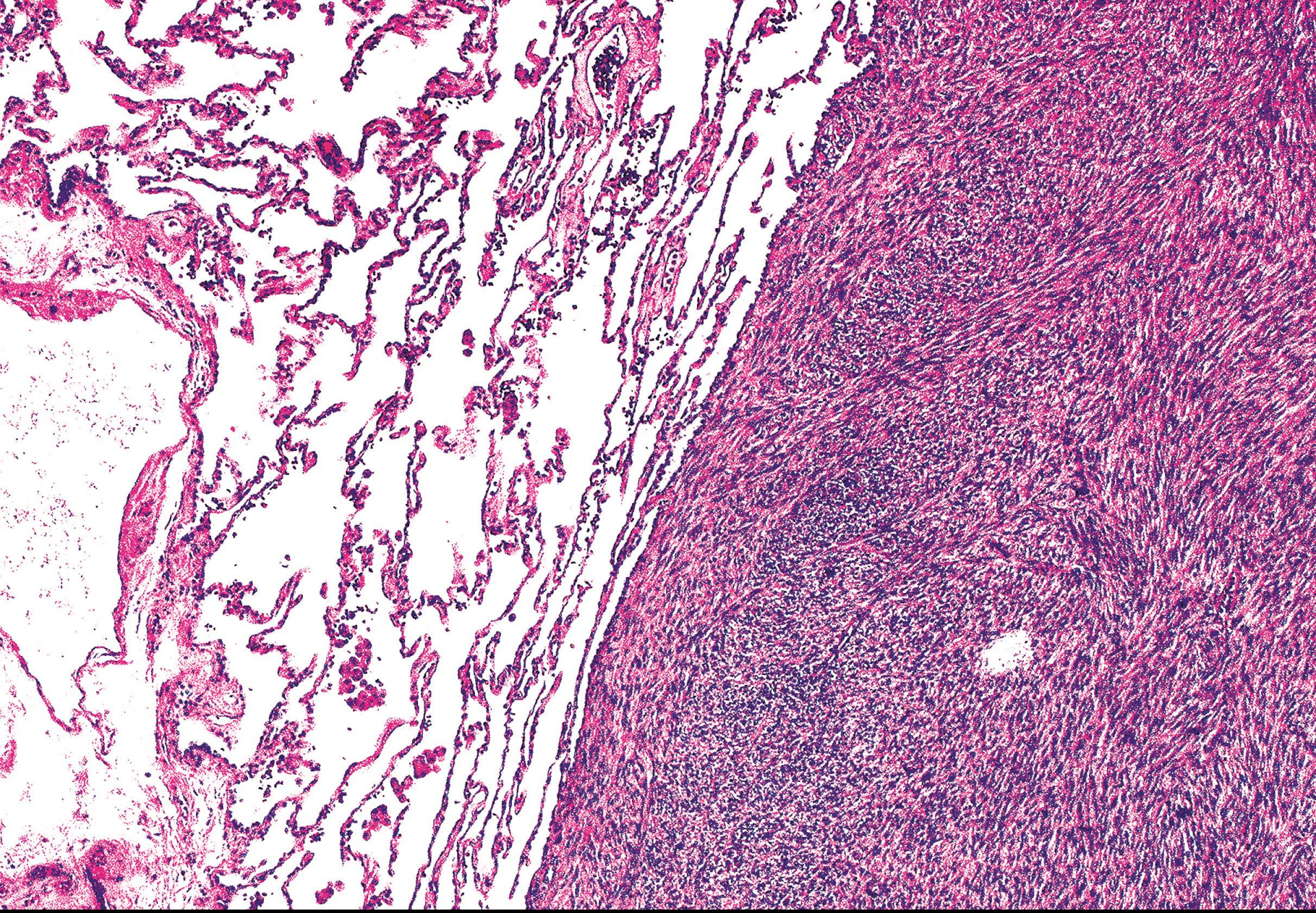




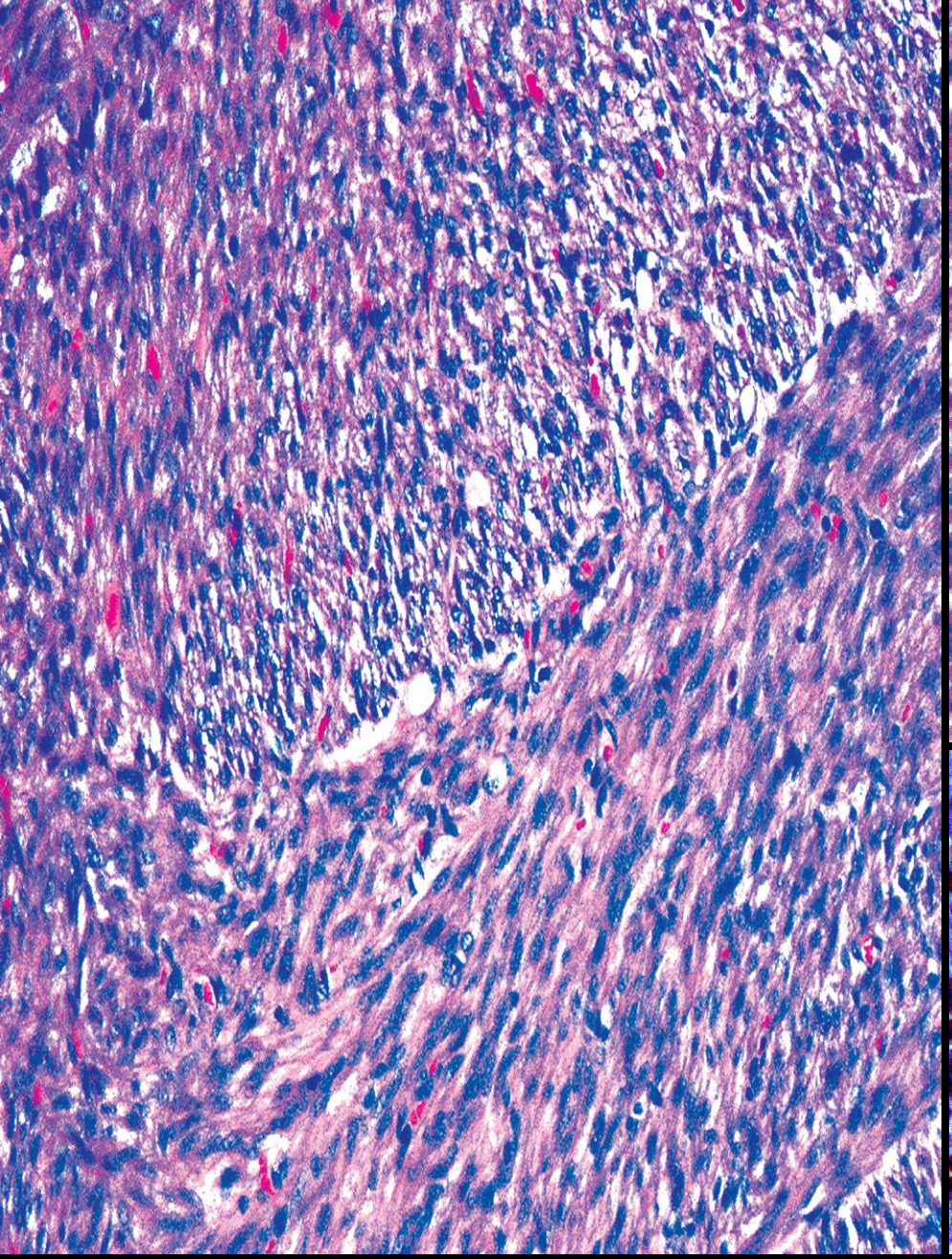
Radiographic Images of "Benign Metastasizing Leiomyoma" of the Lung

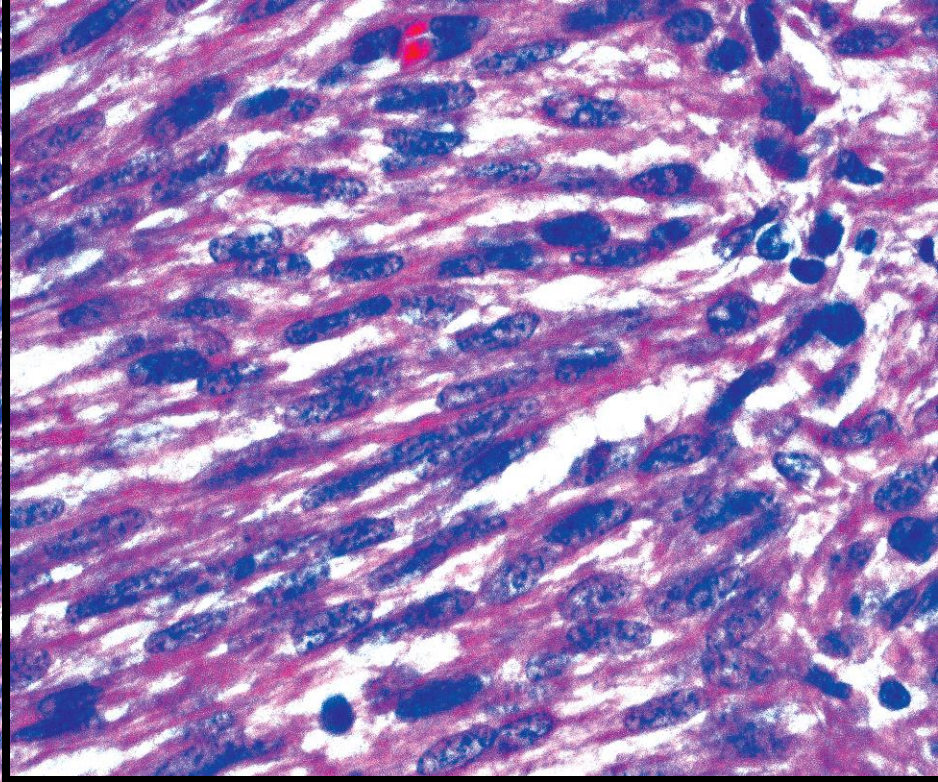
"Benign Metastasizing Leiomyoma" (Multifocal Leiomyomatous Hamartoma)

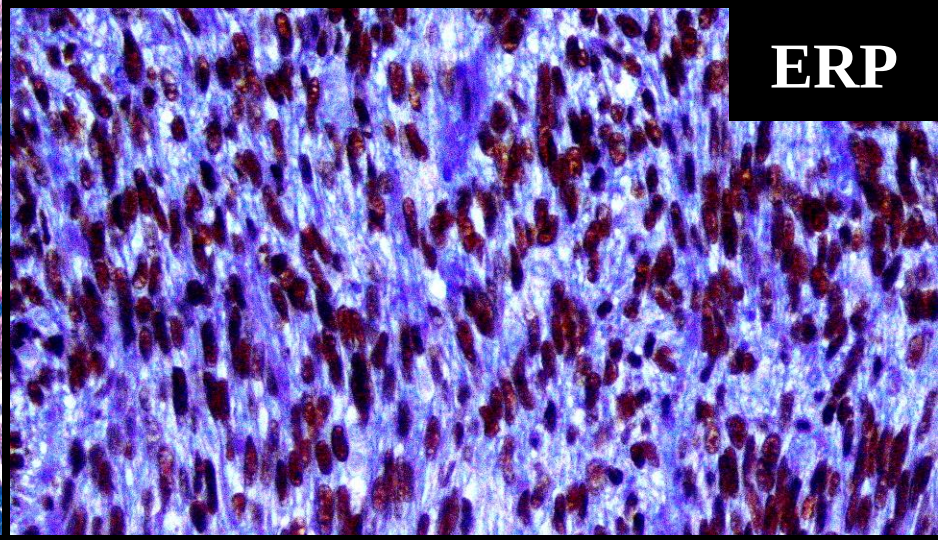
- Typical histological appearance of smooth muscle proliferations, with few if any mitoses and no necrosis
- Bronchiolar epithelium may be intimately entrapped by the spindle-cell proliferation
- Lesional cells are immunoreactive for myogenous markers as well as ERP and PRP



“Benign Metastasizing Leiomyoma” of Lung







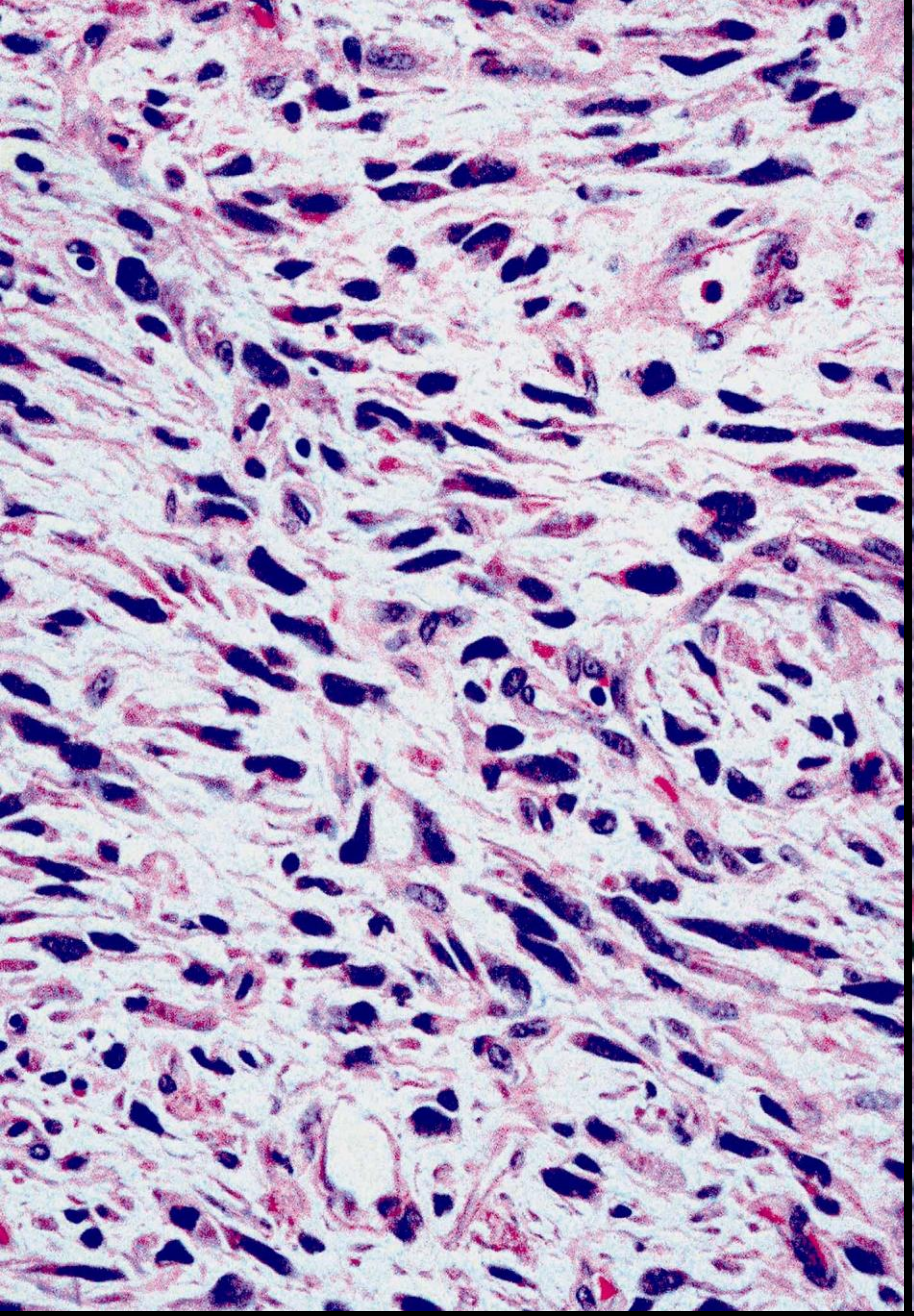
“Benign Metastasizing Leiomyoma” of Lung

"Benign Metastasizing Leiomyoma" (Multifocal Leiomyomatous Hamartoma)

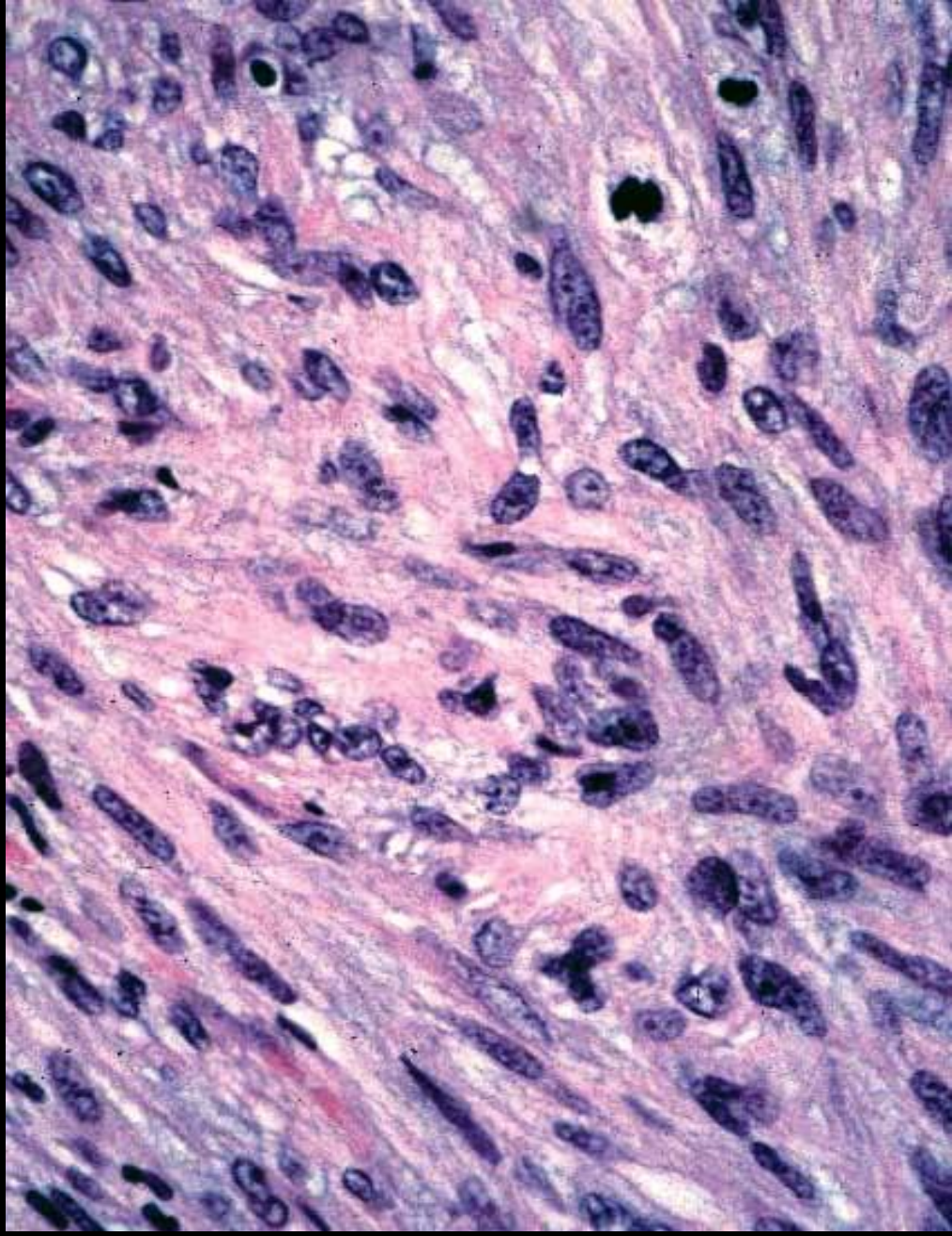
- Despite their alarming appearances, BMLs of the lung are indolent biologically and do not threaten the patient's life
- BMLs cease to proliferate at the menopause, and often regress after that point
- Beneficial clinical results can be obtained from therapy with tamoxifen or aromatase inhibitors

"Benign Metastasizing Leiomyoma:"
Differential Diagnosis

- **Metastatic leiomyosarcoma, from the uterus or soft tissues (mitoses; necrosis; nuclear atypia)**
- **Metastatic sarcomatoid carcinoma with divergent myogenous differentiation (same histologic features as above; keratin-immunoreactivity)**



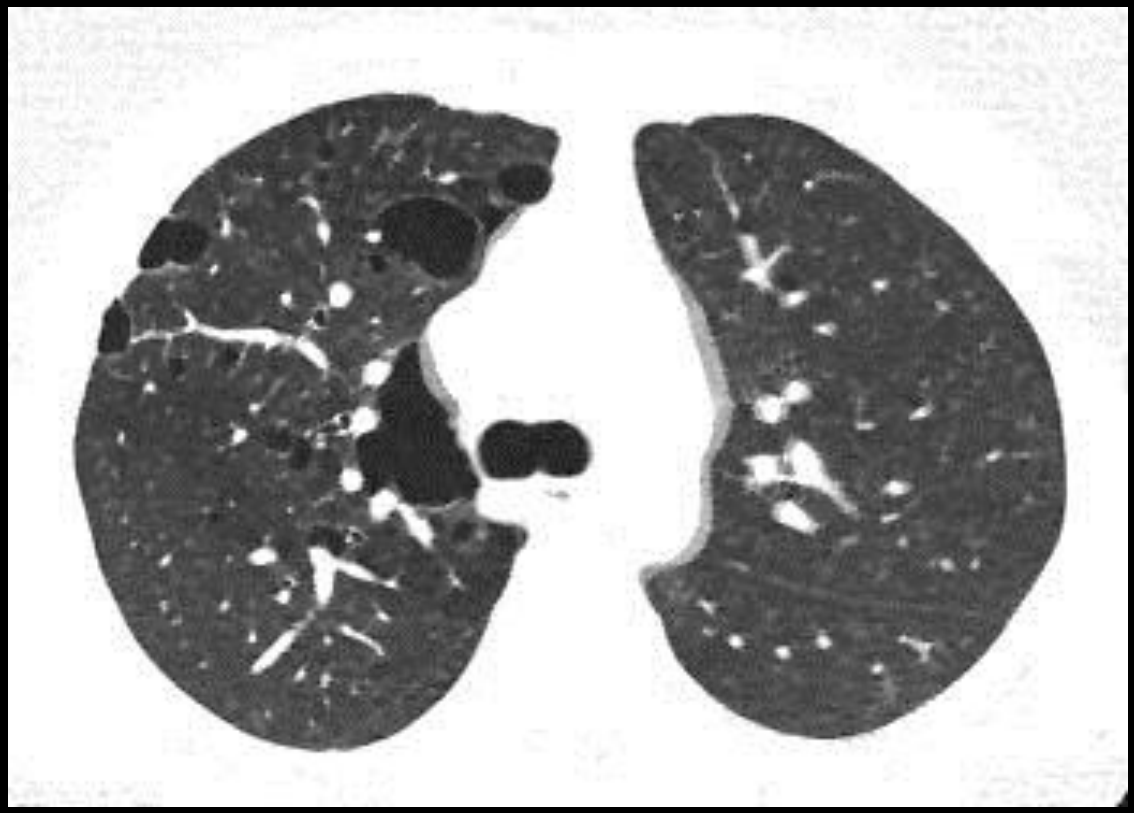
Sarcomatoid Carcinoma



Metastatic Leiomyosarcoma

Cystic Fibrohistiocytic Tumor of the Lung

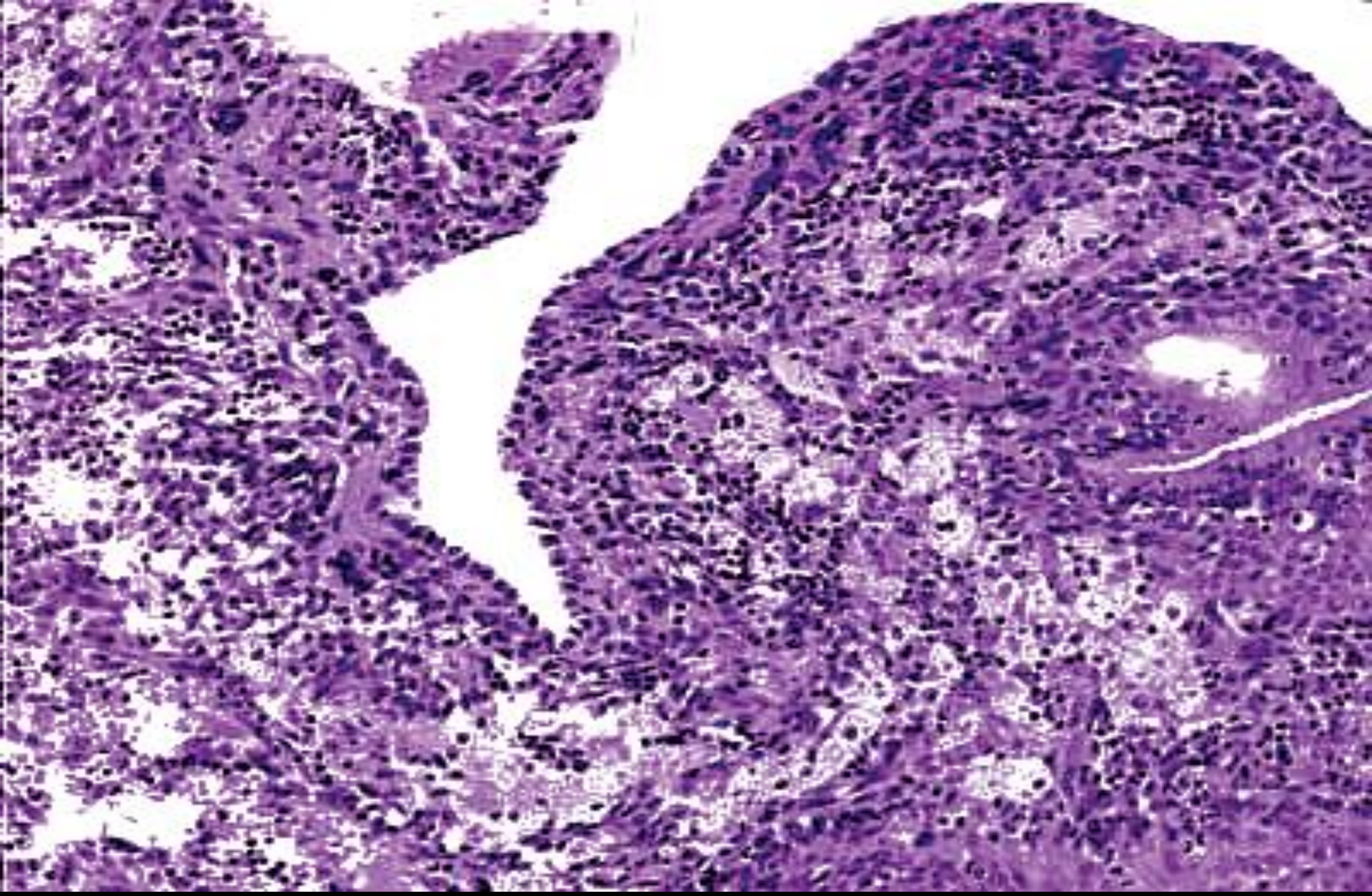
- Rare lesion; <25 cases reported thus far
- Potentially-multifocal cystic tumor of the lungs
- Patients may be asymptomatic or present with pneumothorax or shortness of breath



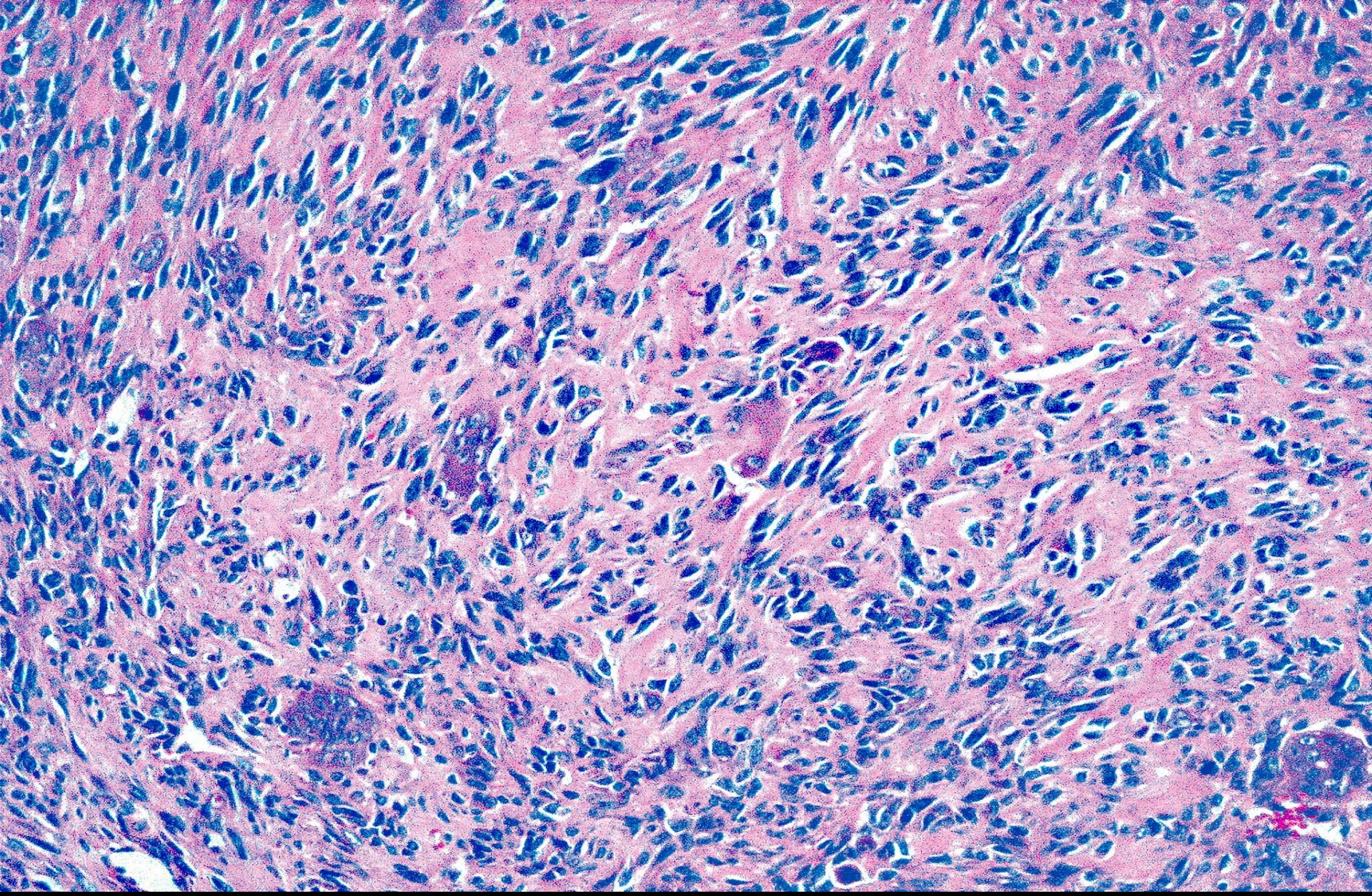
Multifocal Cystic Fibrohistiocytic Tumor of Lung– CT Scan

Cystic Fibrohistiocytic Tumor of the Lung

- Cystic spaces in lung parenchyma, mantled by a proliferation of relatively-bland spindle cells and histiocyte-like elements
- Cysts may by lined by bronchiolar epithelium, bland squamous cells, or type II pneumocytes
- Lumina of cysts may contain erythrocytes or hemosiderin



Multifocal Cystic Fibrohistiocytic Tumor of Lung– CT Scan



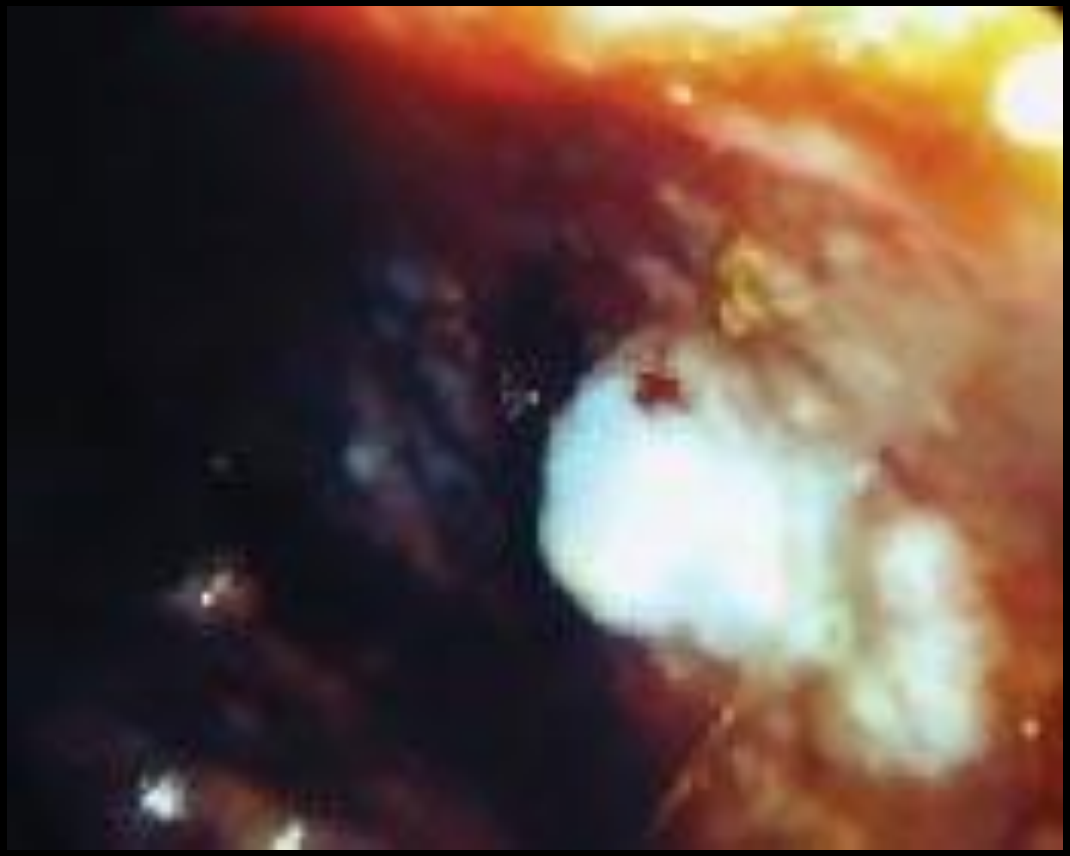
Multifocal Cystic Fibrohistiocytic Tumor of Lung

Cystic Fibrohistiocytic Tumor of the Lung: Differential Diagnosis & Behavior

- **Principal differential diagnostic consideration is that of metastatic low-grade fibrohistiocytic tumors of skin and soft tissue; these are typically obvious clinically and therefore largely academic**
- **Behavior of CFTL is still uncertain–included in the benign group of pulmonary tumors tentatively**

Adenomatoid Tumor of Pleura

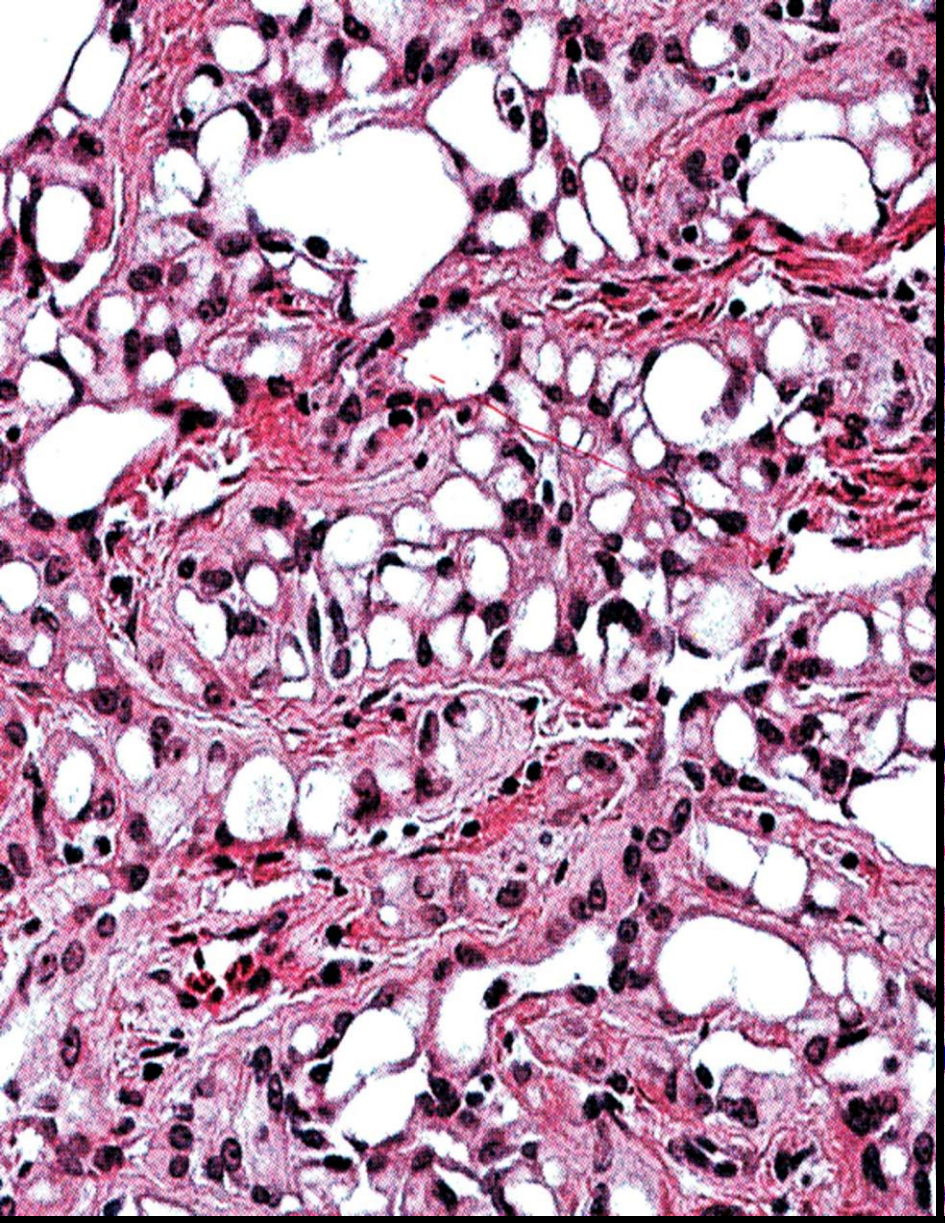
- **Asymptomatic, incidental findings at surgery or thoracoscopy done for other reasons**
- **All reports have been in middle-aged or elderly adults**
- **Unencapsulated pleural-based nodules measuring up to 2.5 cm in greatest dimension**

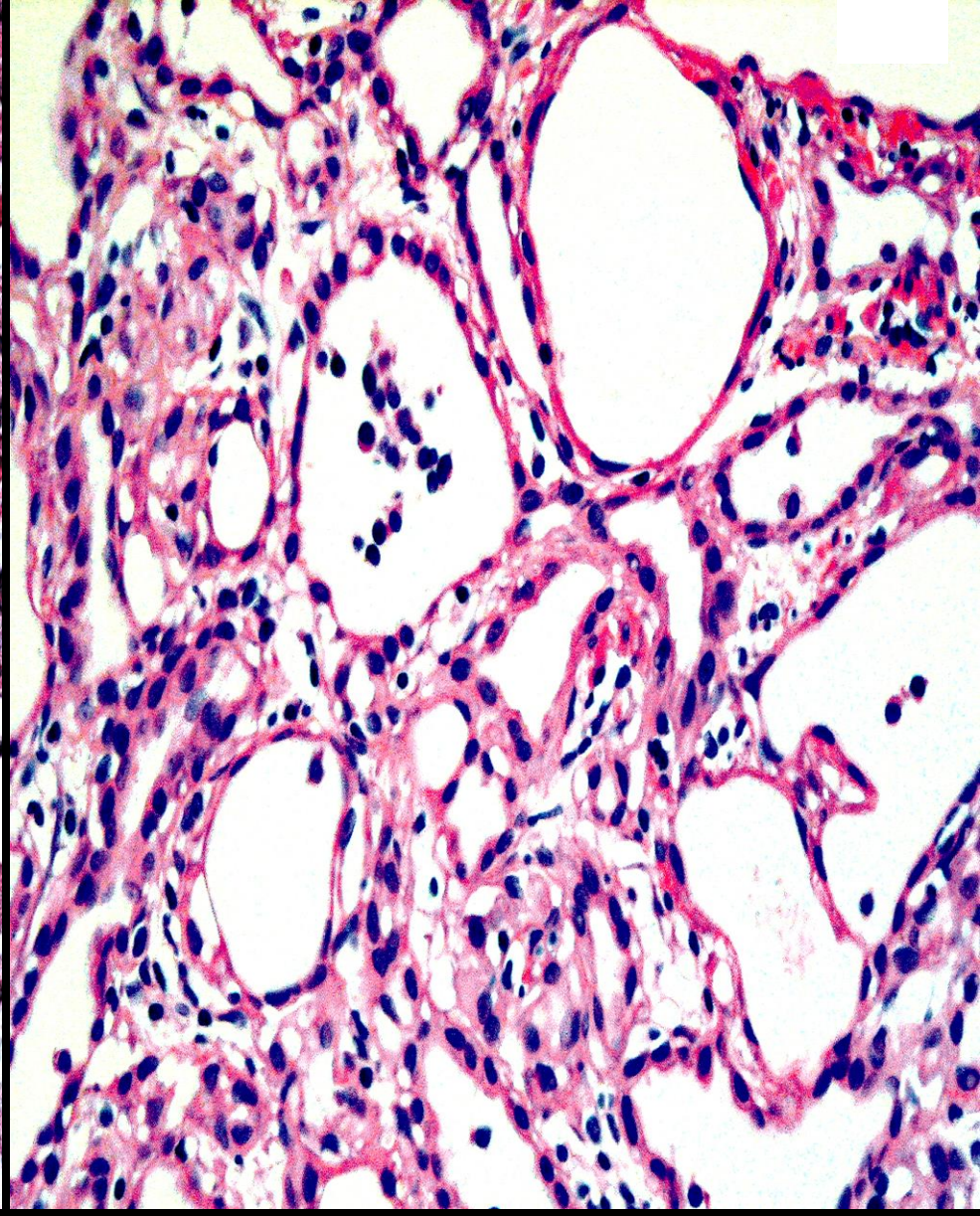


Adenomatoid Tumor of Pleura at Thoracoscopy

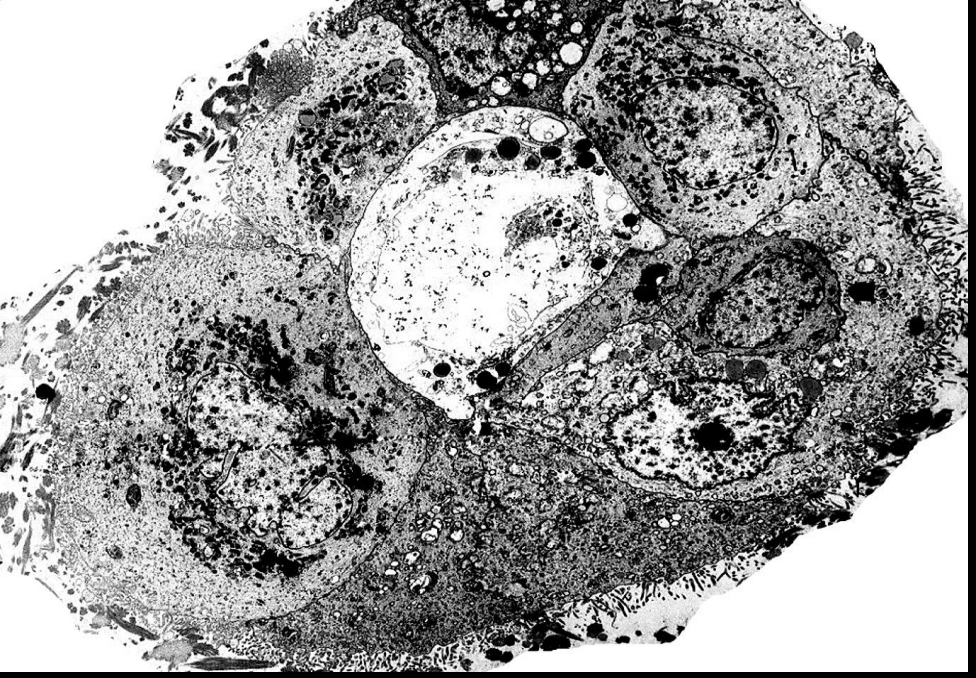
Adenomatoid Tumor of Pleura

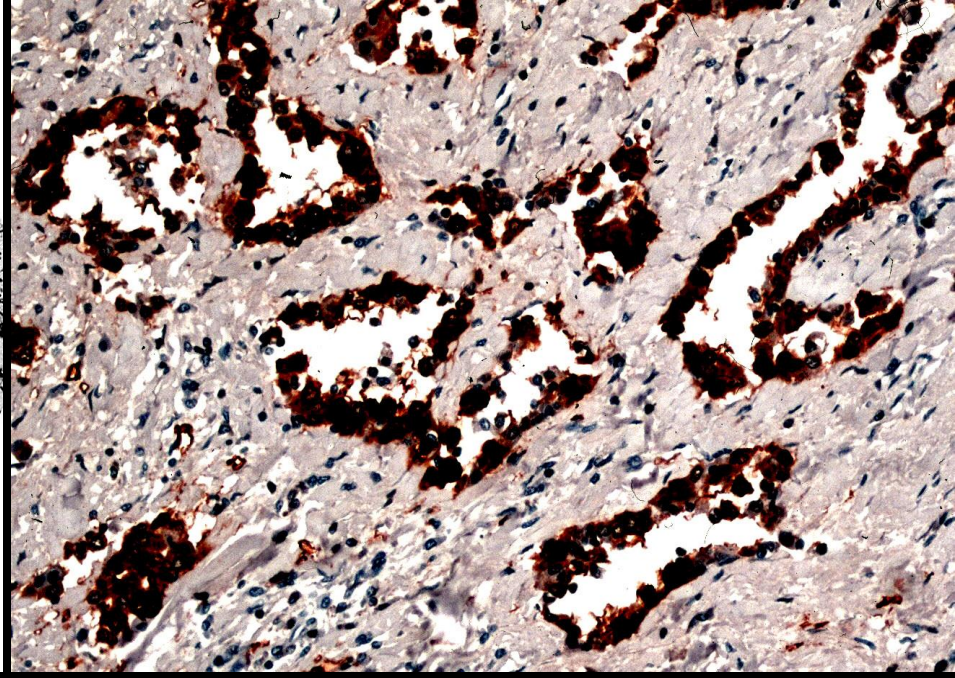
- Interanastomosing microcystic profiles lined by bland low-cuboidal cells
- No mitoses or necrosis
- Analogous in every way to adenomatoid tumors of the genitals
- Mesothelial profile by immunohistochemistry and electron microscopy

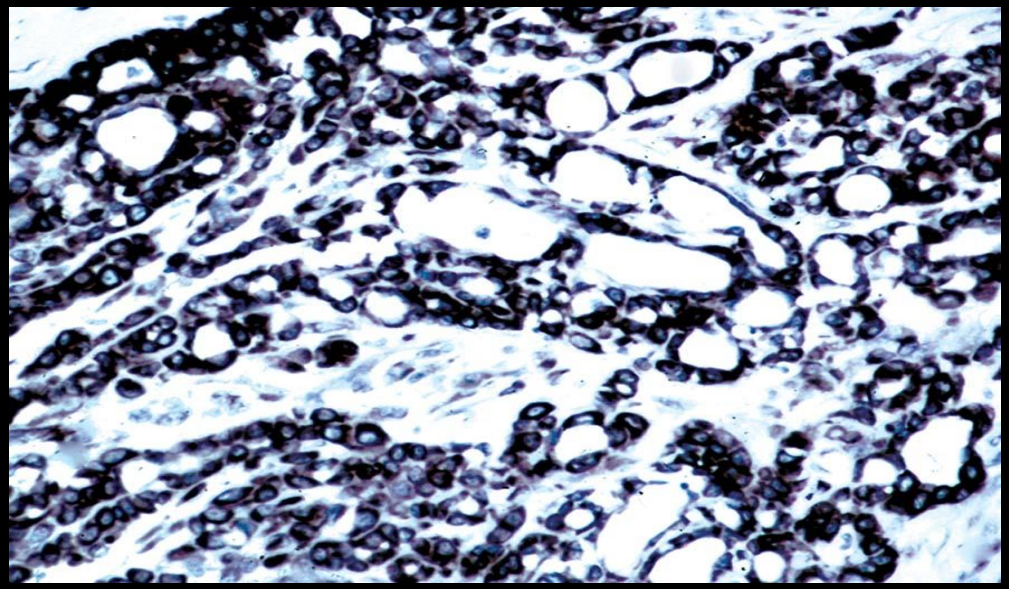




Adenomatoid Tumor of Pleura



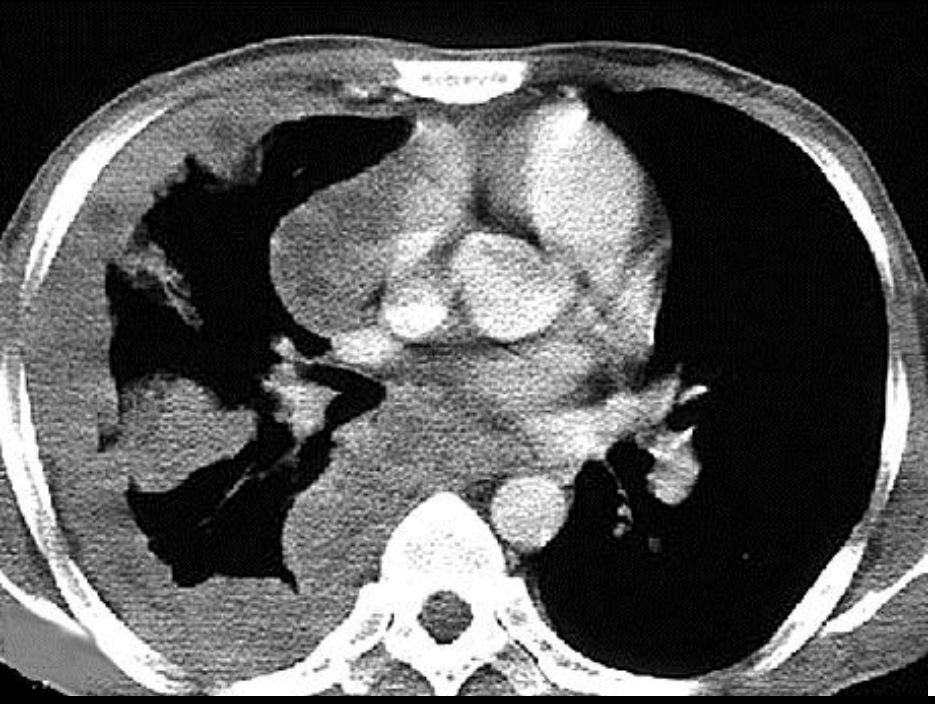


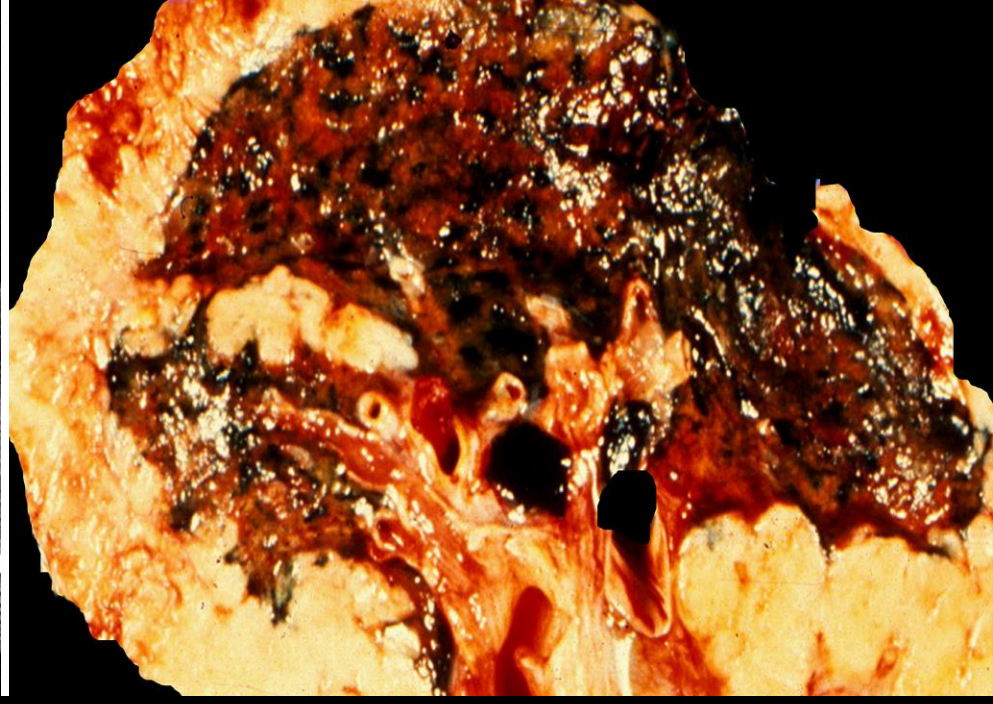


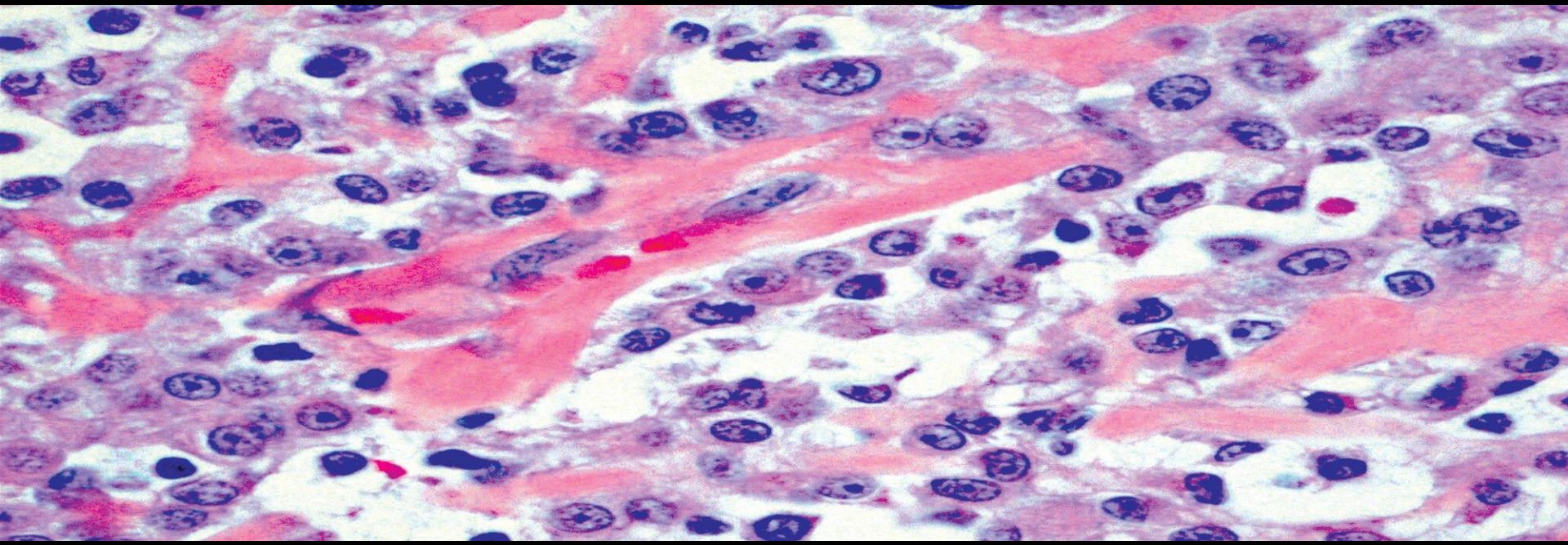
Adenomatoid Tumor of Pleura– EM & Calretinin/CK 5-6 Immunostains

Adenomatoid Tumor of Pleura:
Differential Diagnosis

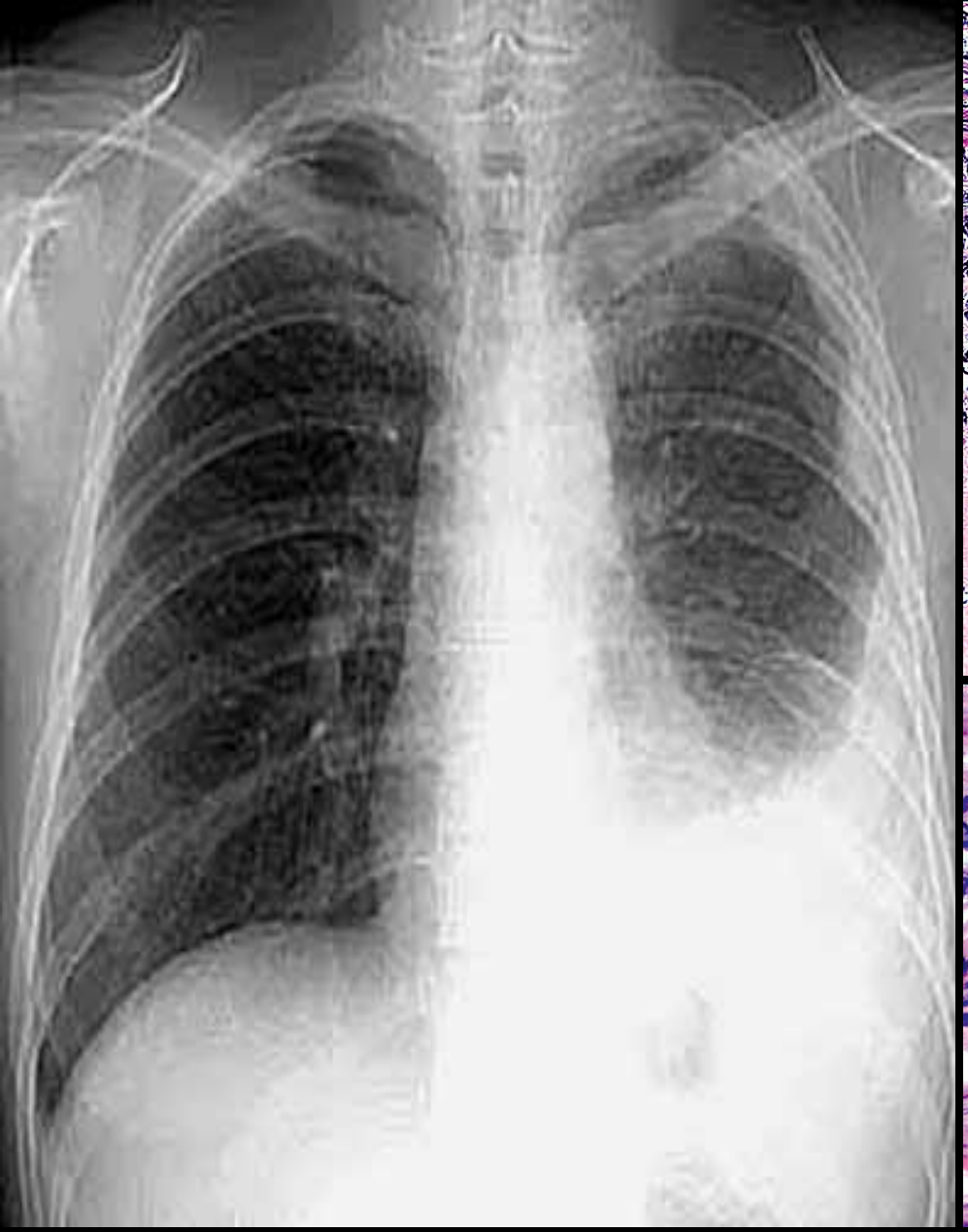
- **Mesothelioma– Usually multifocal & symptomatic; large confluent masses; nuclear atypia and invasion of underlying tissue**
- **Epithelioid Hemangioendothelioma– Usually infiltrative & symptomatic; Calretinin & WT1-negative; Reactive for *factor VIII-related antigen***

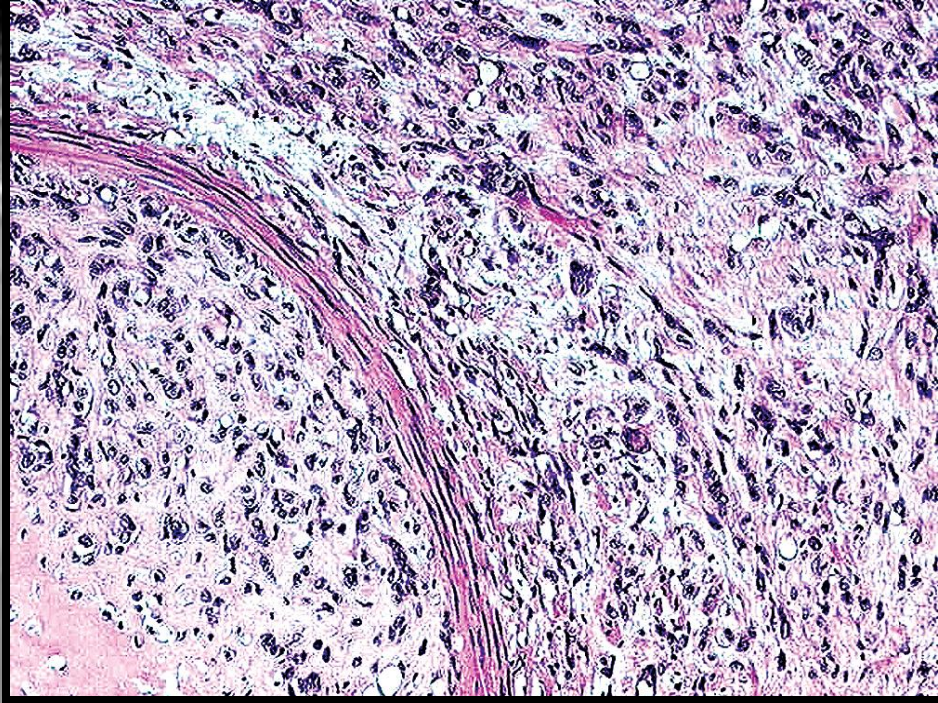


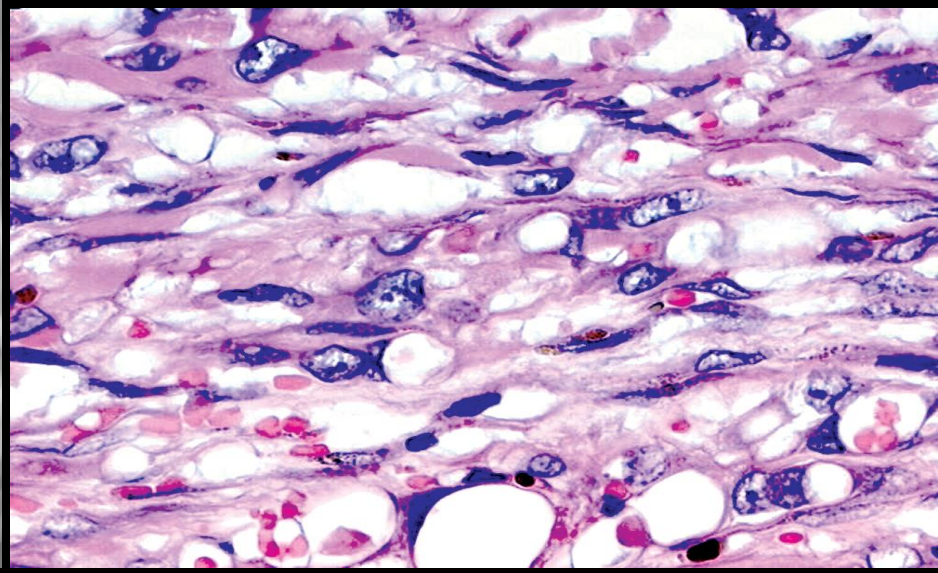




Epithelioid Mesothelioma– CT scan; Gross & Microscopic Images



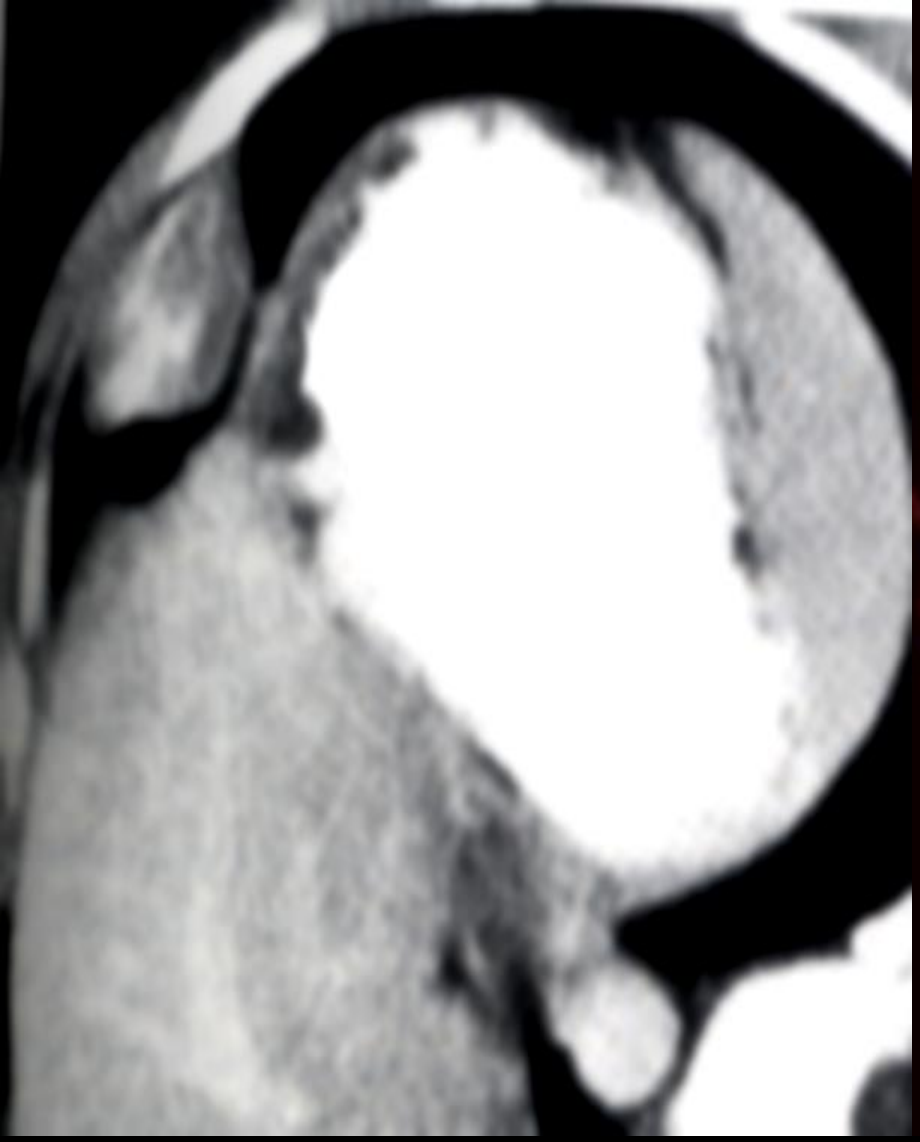


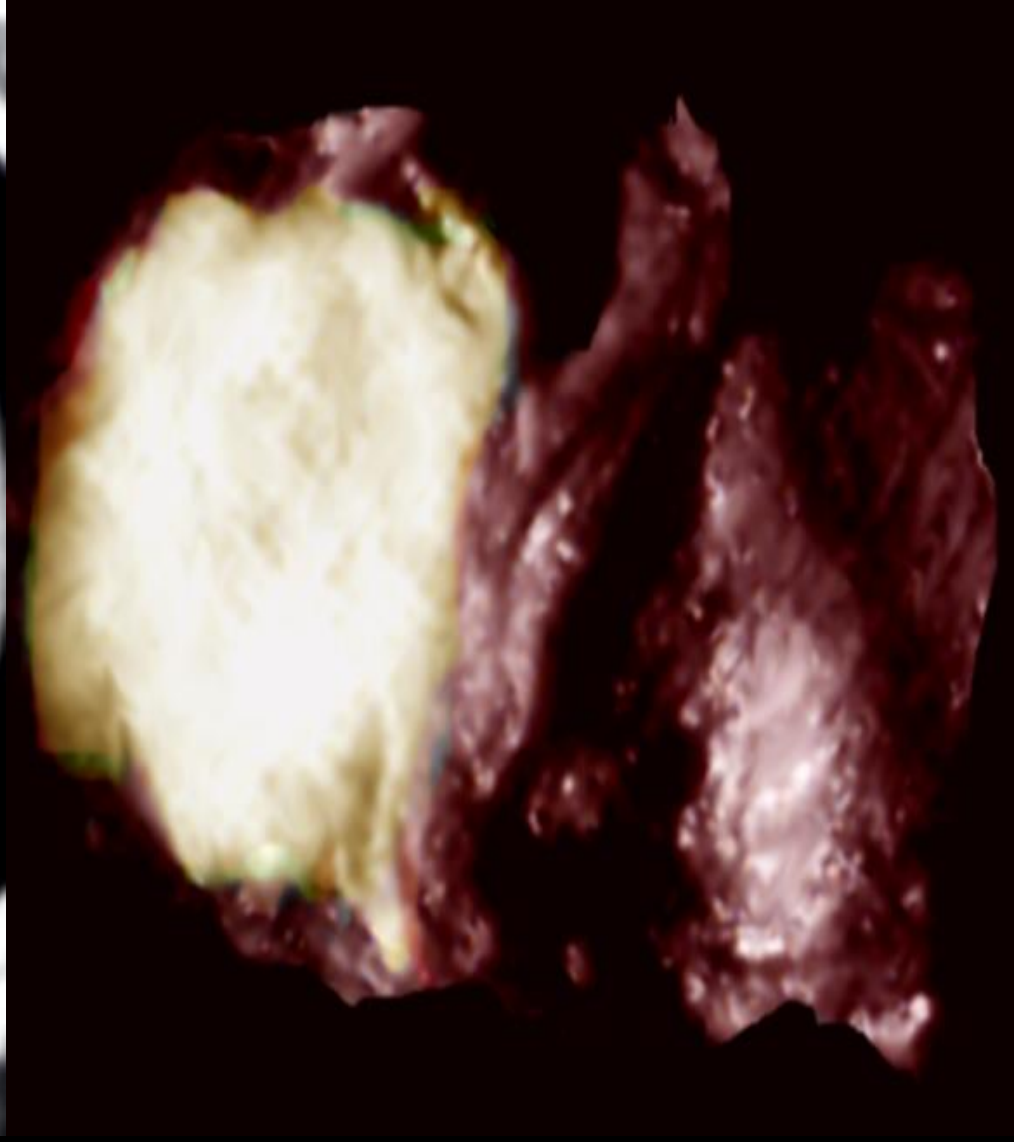


Pleural Epithelioid Hemangioendothelioma

Calcifying Fibrous Pseudotumor of Pleura

- **Analogous to CFPT of soft tissue, as described by Rosenthal & Abdul-Karim**
- **Seen in adults; often asymptomatic but may be accompanied by chest pain; not associated with asbestos exposure**
- **Well-demarcated, partially-calcified pleural nodules, measuring up to 12 cm in greatest dimension**

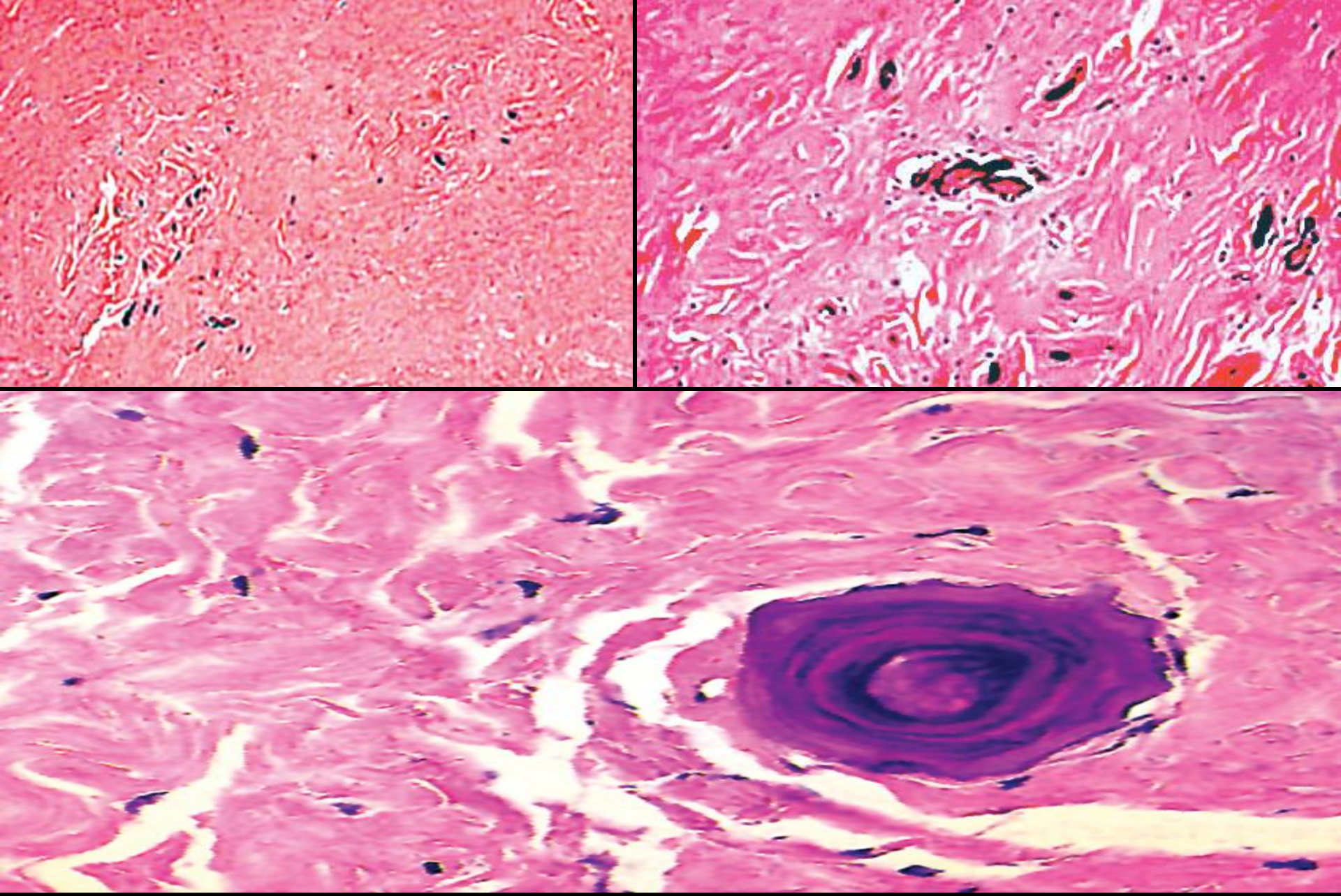




Calcifying Fibrous Pseudotumor of Pleura– CT Scan & Gross Image

Calcifying Fibrous Pseudotumor of Pleura

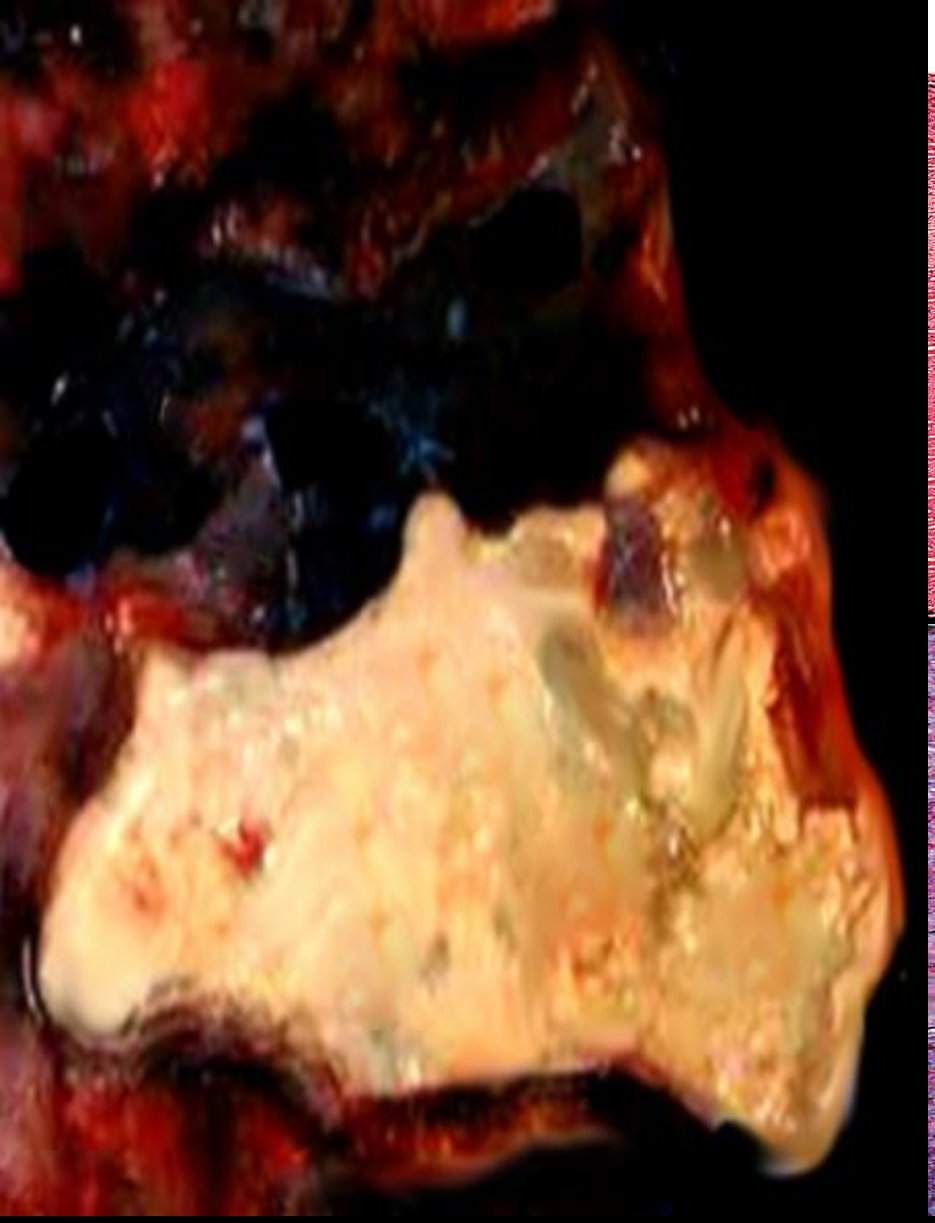
- **Sclerotic paucicellular stroma, in which foci of dystrophic calcifications reside**
- **Psammomatous-type calcifications are also common**
- **No areas of inflammation, hypercellularity, or nuclear atypia**

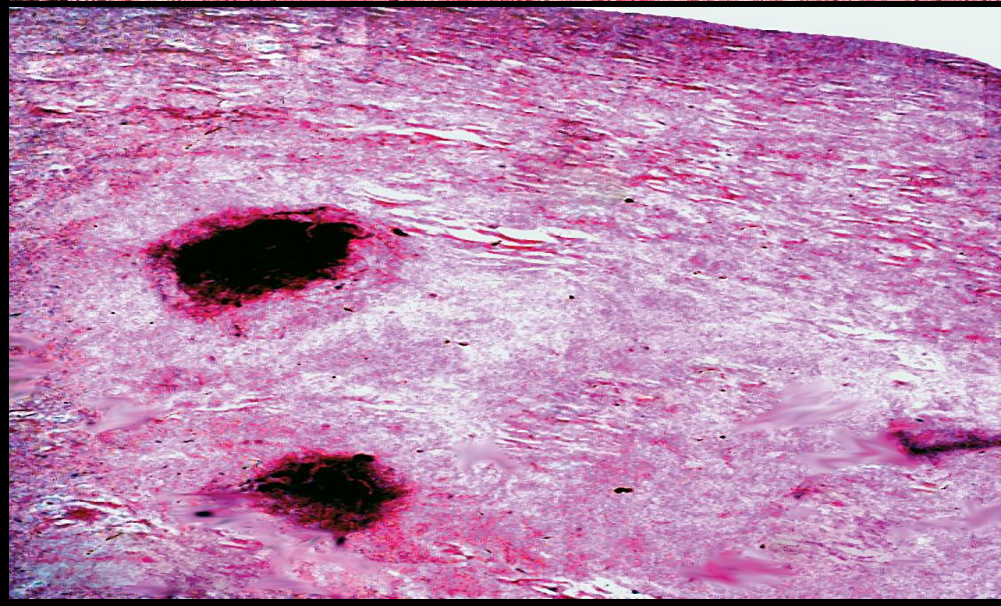


Calcifying Pseudotumor of Pleura

Calcifying Fibrous Pseudotumor of Pleura: *Differential Diagnosis*

- **Tumefactive pleural plaque (laminated; no concentric psammomatous calcifications)**
- **Fibrous meningioma of lung (… a conceptual stretch)**





Tumefactive Fibrohyaline (Asbestos) Pleural Plaque

"Borderline" Tumors of the Lung: General Features

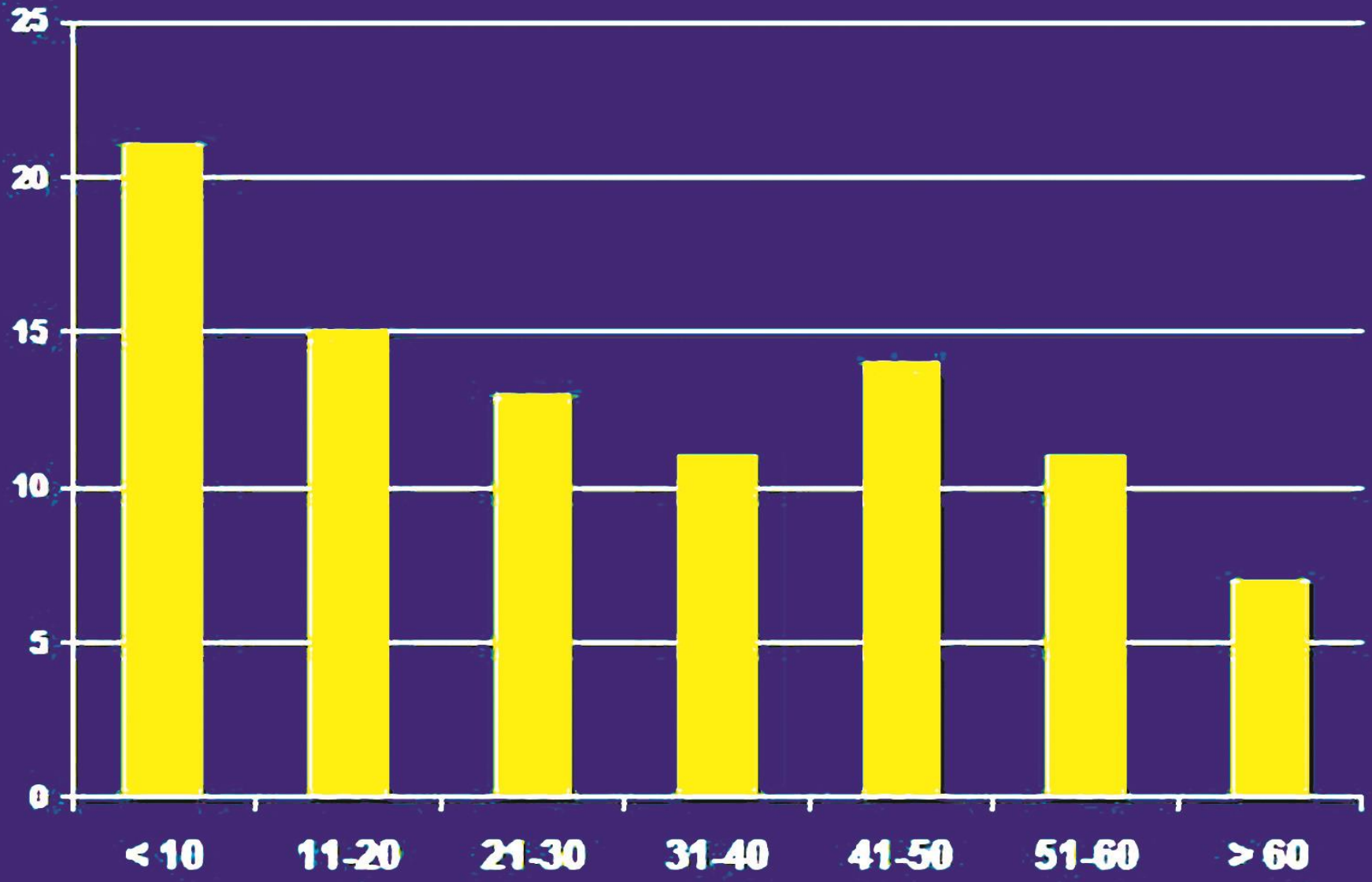
- Indolent in the vast majority of cases, with local recurrence being the principal adverse event
- Rare examples of metastasis

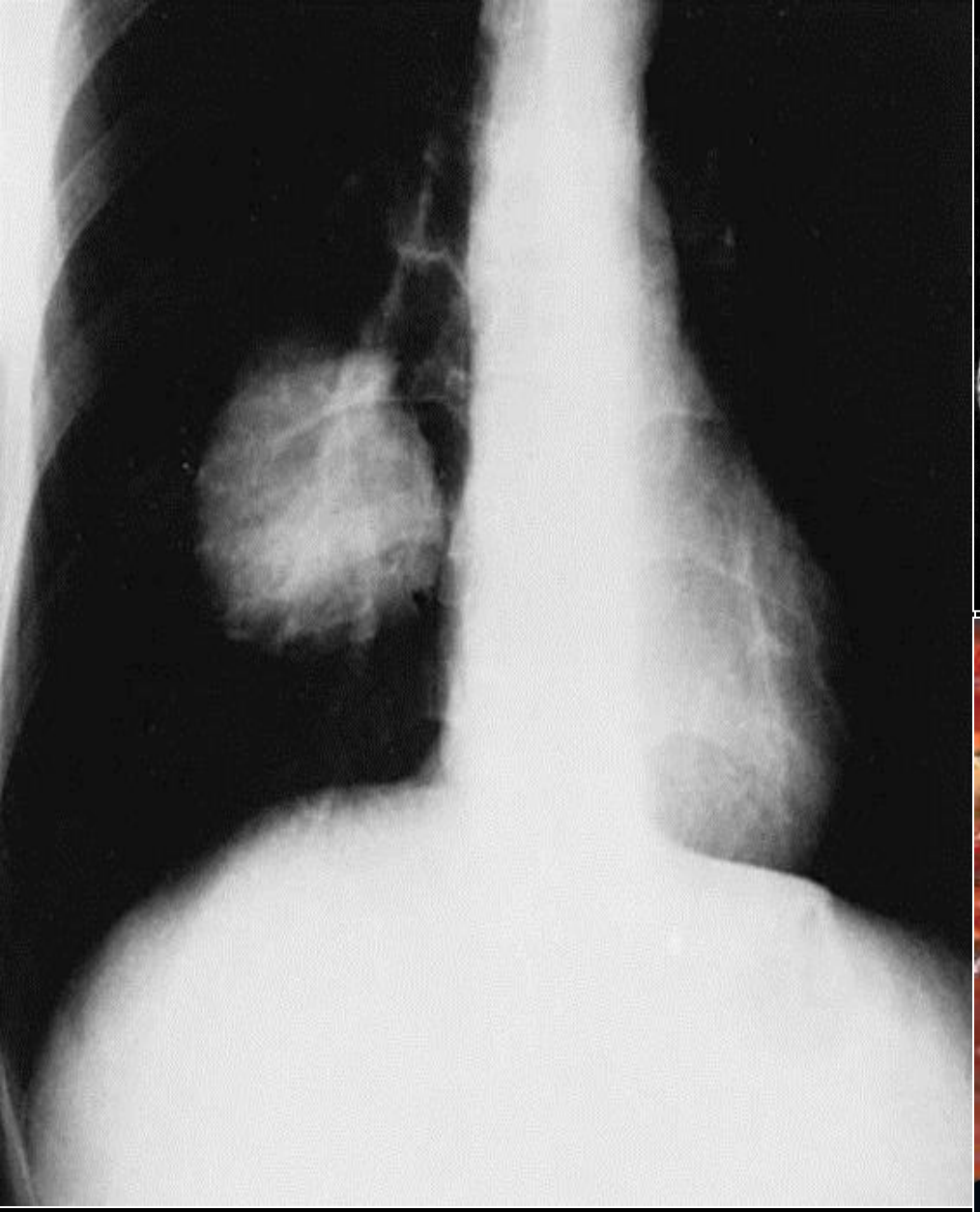
Inflammatory Myofibroblastic Tumor (IMT) of Lung

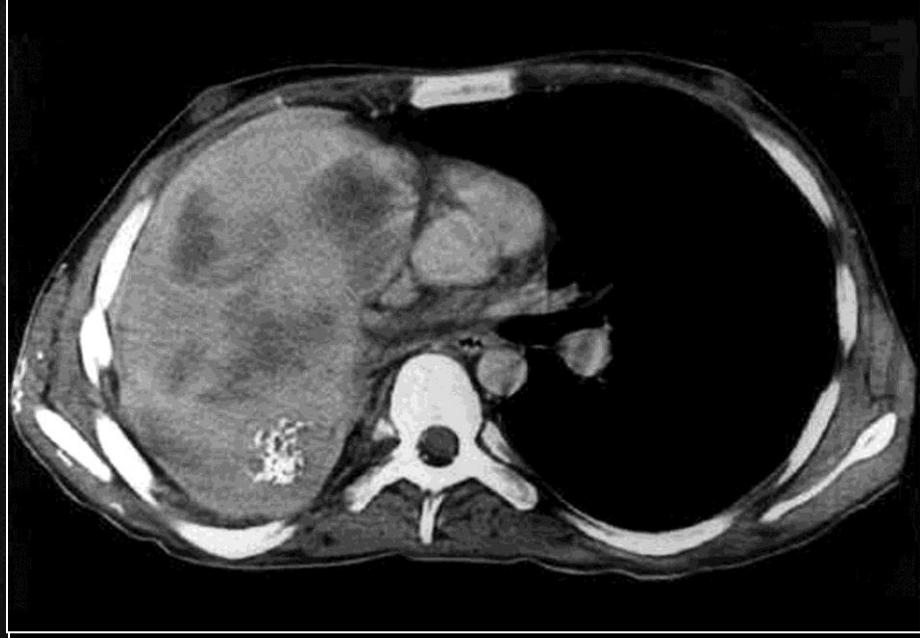
- Formerly called "inflammatory pseudotumor"– there are 2 forms of that lesion, one of which is clonal and neoplastic (this one, now called IMT) and the other being reactive (probably tumefactive organizing pneumonia in most instances)
- Lung is the most common anatomic site for IMT
- Predominant in patients <30 yrs old, but can be seen at any age
- May be associated with paraneoplastic findings such as anemia, fever, weight loss, dysglobulinemias, leukothrombocytosis, and elevation in erythrocyte sedimentation rate
- Other cases present with cough, chest pain, hemoptysis, or they may be asymptomatic

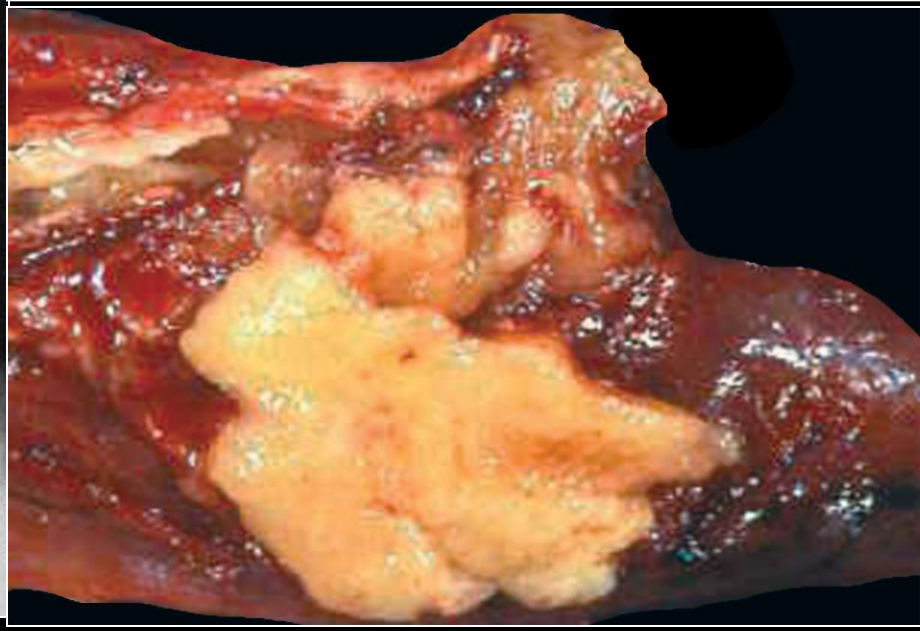
Inflammatory Myofibroblastic Tumor

Age Distribution*





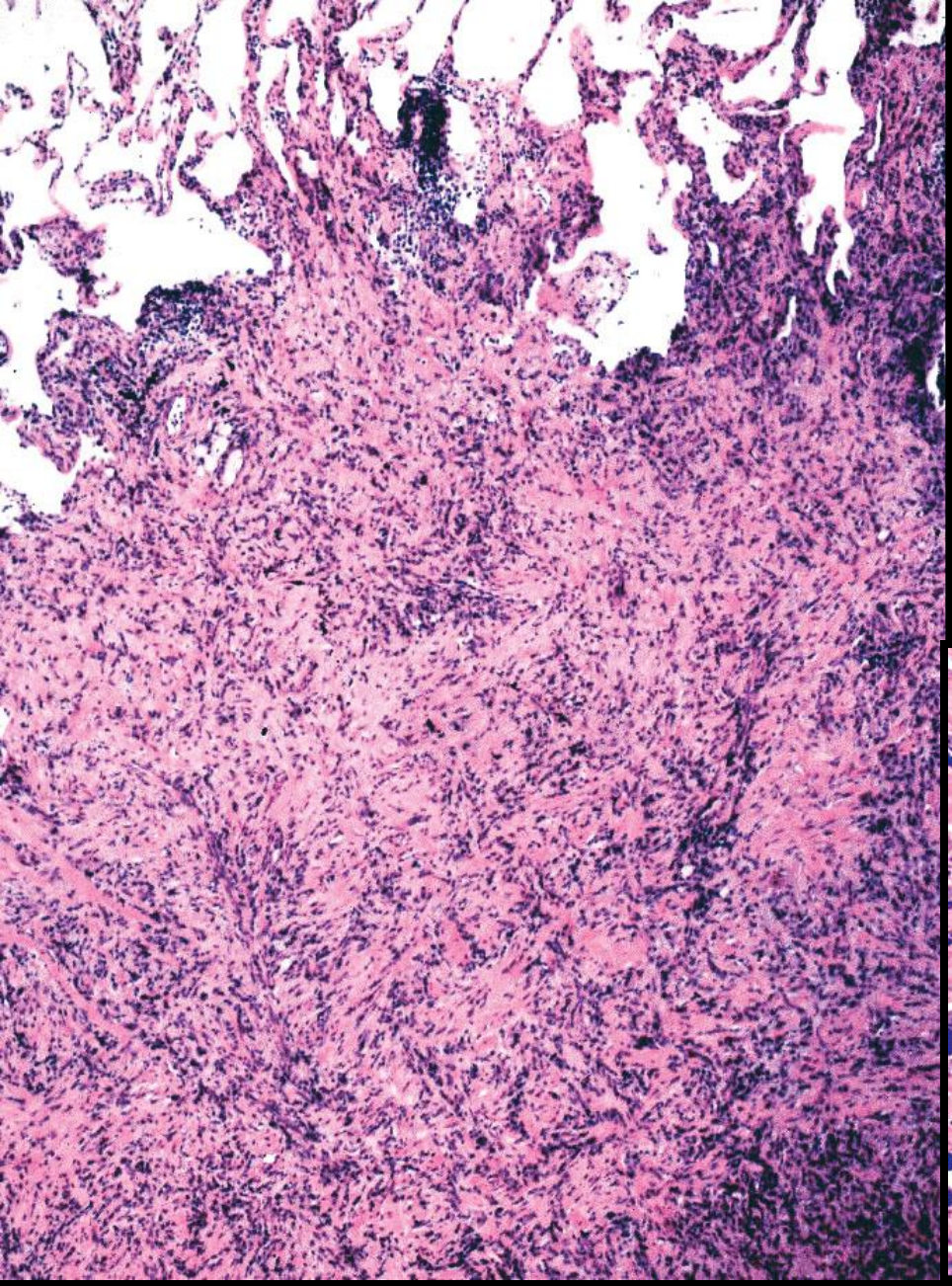


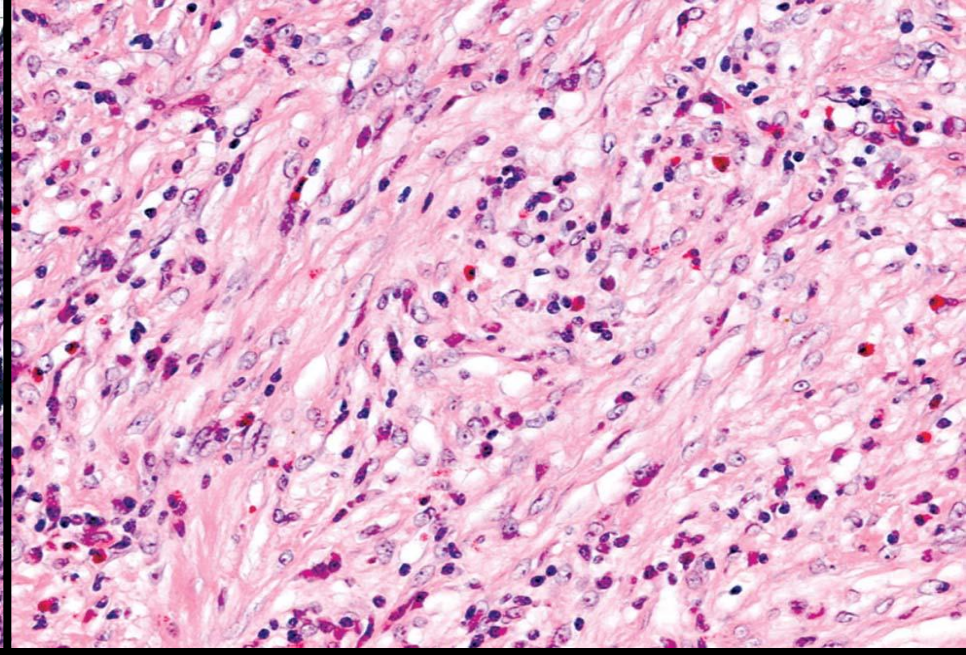


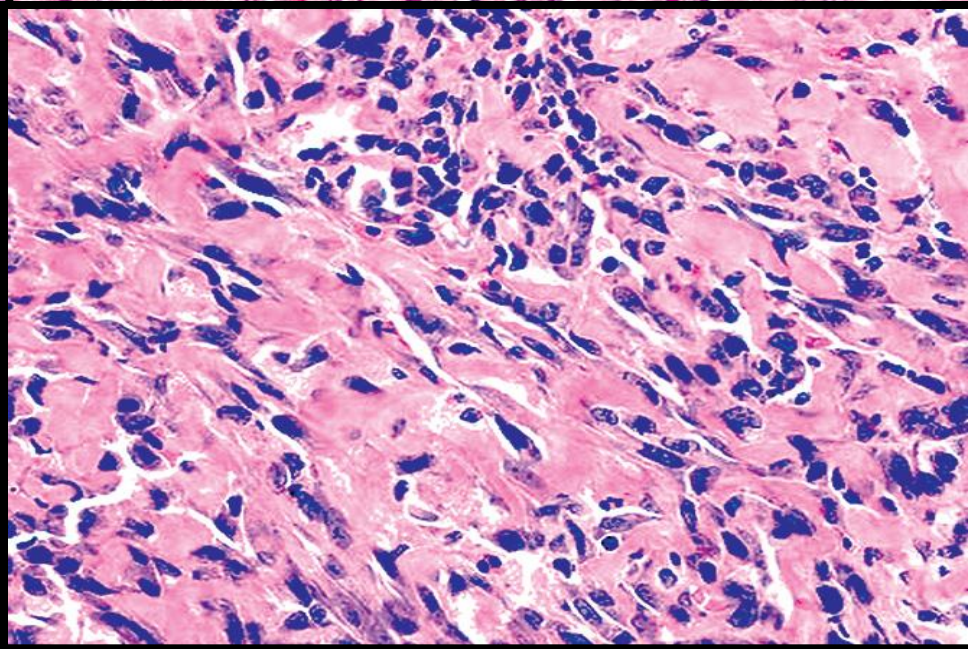
Inflammatory Myofibroblastic Tumor of Lung– CXR & Gross Images

Inflammatory Myofibroblastic Tumor (IMT) of Lung

- Relatively bland spindle-cell proliferation, variably populated by lymphocytes, plasma cells, eosinophils, and histiocytes
- Vaguely-fascicular growth pattern; infiltration of bronchial walls, blood vessels, and pleura may be seen
- Mitotic activity is easily seen; foci of necrosis may be apparent





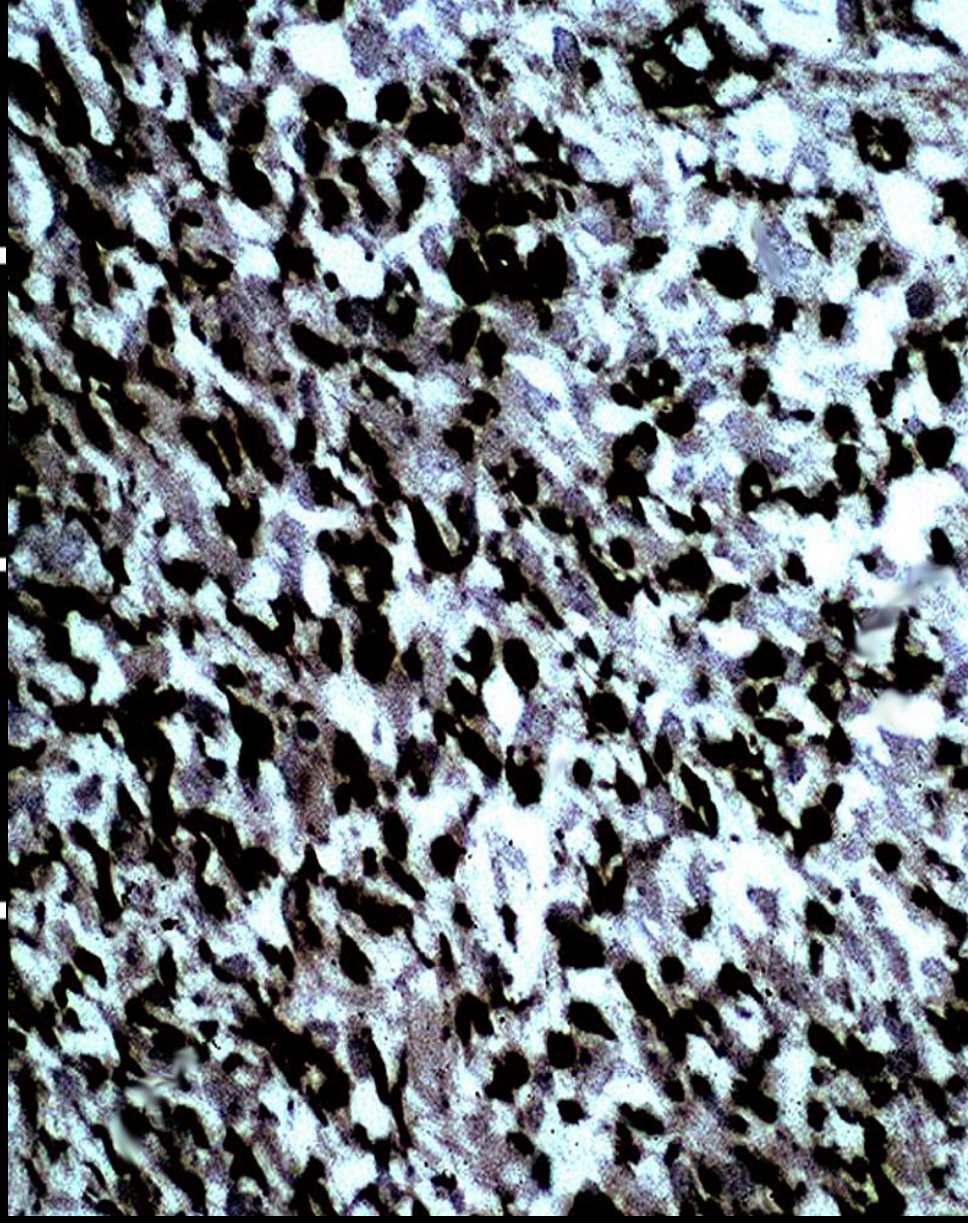


Inflammatory Myofibroblastic Tumor of Lung

Inflammatory Myofibroblastic Tumor (IMT) of Lung

- **Neoplastic spindle-cells in IMT show cytogenetic aberrations in chromosome 2p23 in 40% of cases (usually translocations)**
- **This is reflected by immunoreactivity for *ALK-1*/p80 protein, as seen in some anaplastic large-cell lymphomas**

Chromosome 2p23 aberrations

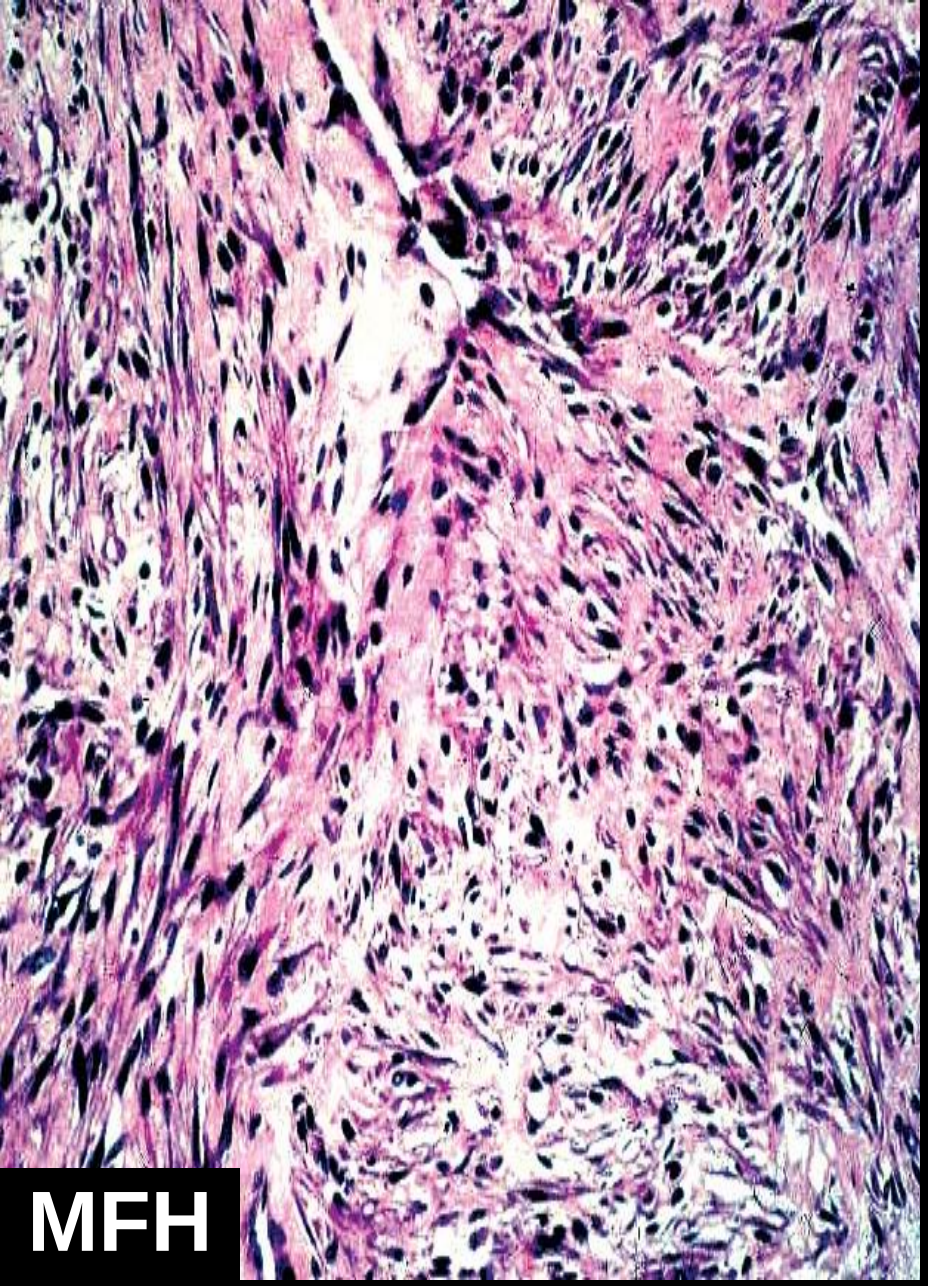


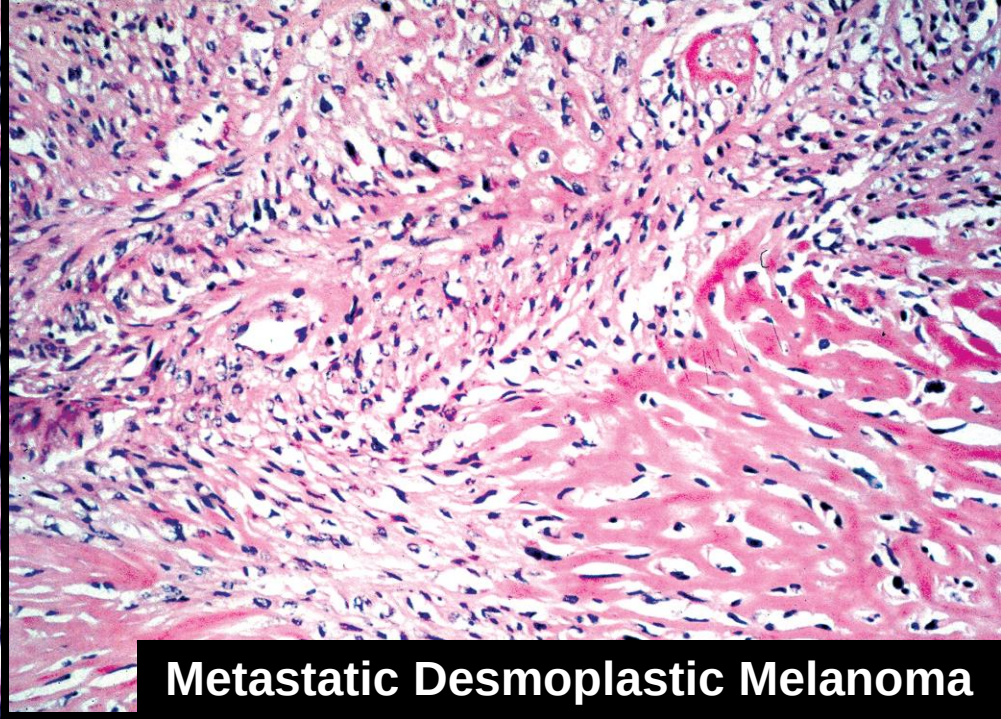
ALK-1-immunoreactivity in IMT

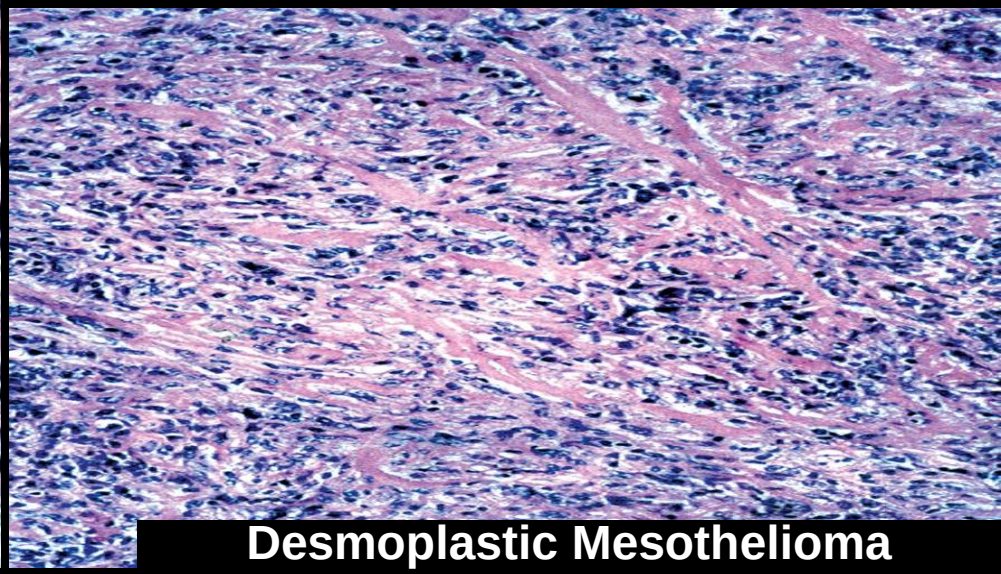
Inflammatory Myofibroblastic Tumor of Lung

Inflammatory Myofibroblastic Tumor (IMT) of Lung: *Behavior & Differential Diagnosis*

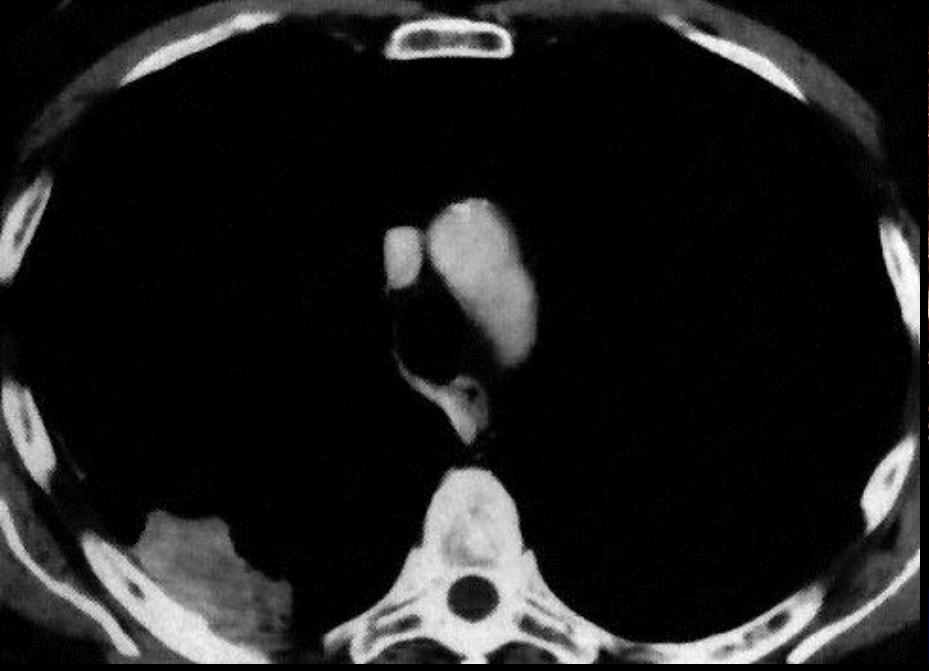
- **Lesions may remain stable, progress slowly, recur after surgery, or, rarely metastasize**
- **Involvement of pleura, hilar structures, diaphragm, or mediastinum is an adverse prognostic finding in IMT**
- **Differential diagnosis is principally with low-grade sarcomas, metastatic desmoplastic melanoma (S100+), localized spindle-cell & inflammatory mesothelioma (CK+), and inflammatory sarcomatoid carcinoma (CK+) (especially in adults)**

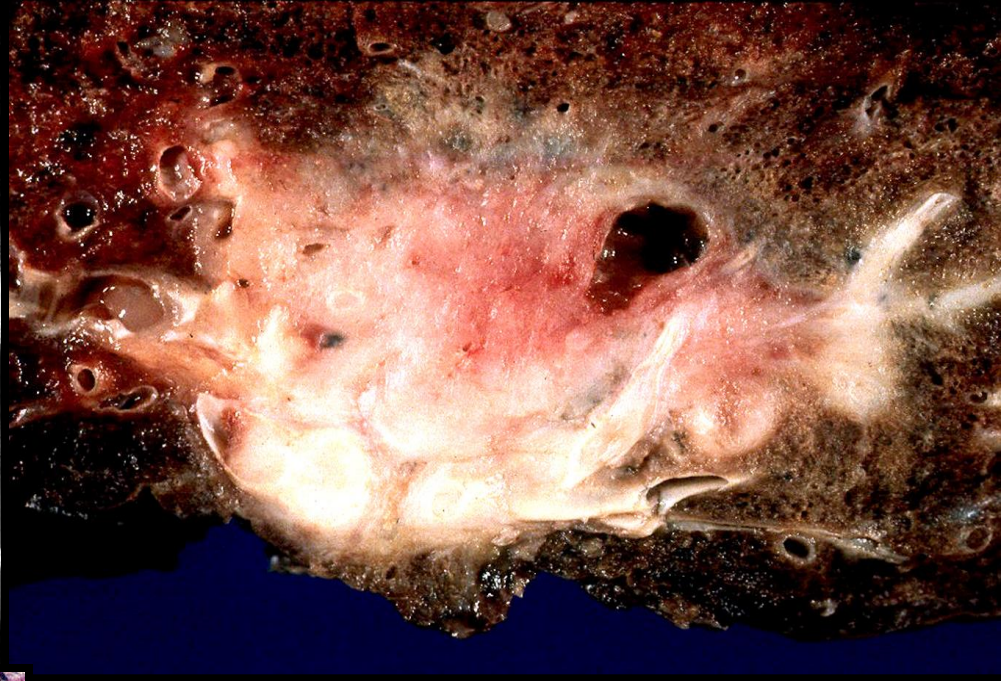


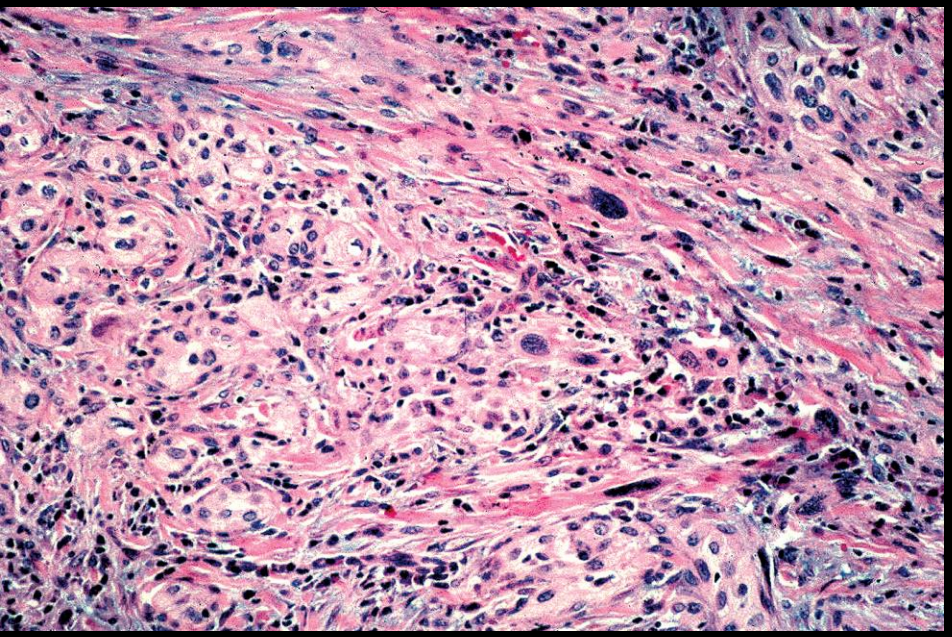




Other Spindle-Cell Malignancies of Lung & Pleura





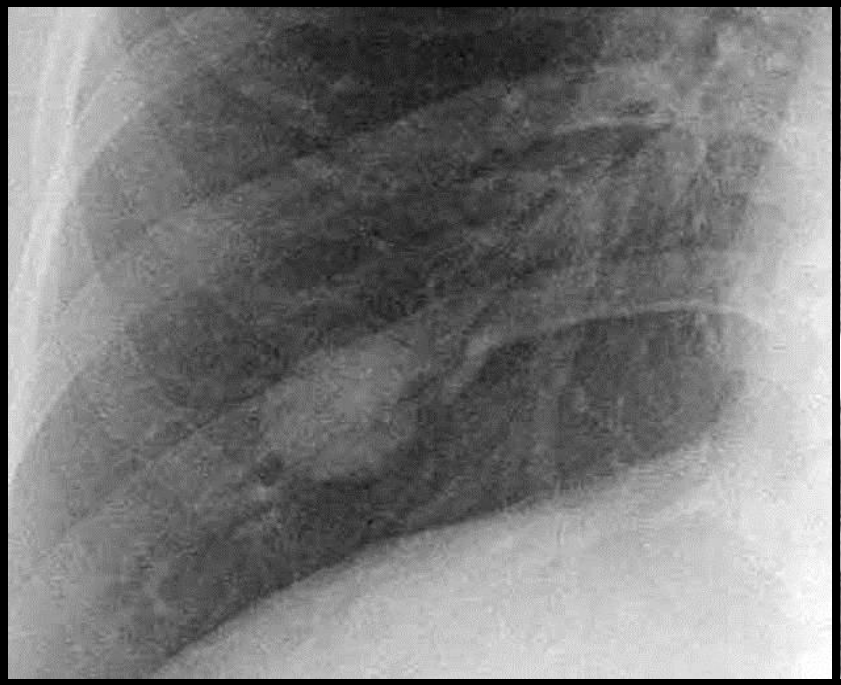


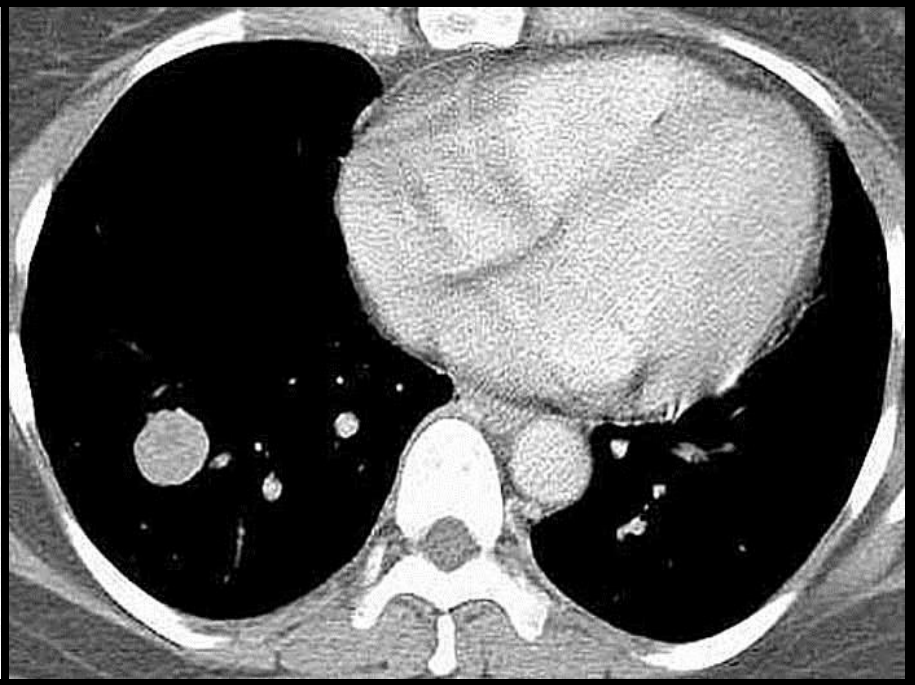
Inflammatory Sarcomatoid Carcinoma of Lung

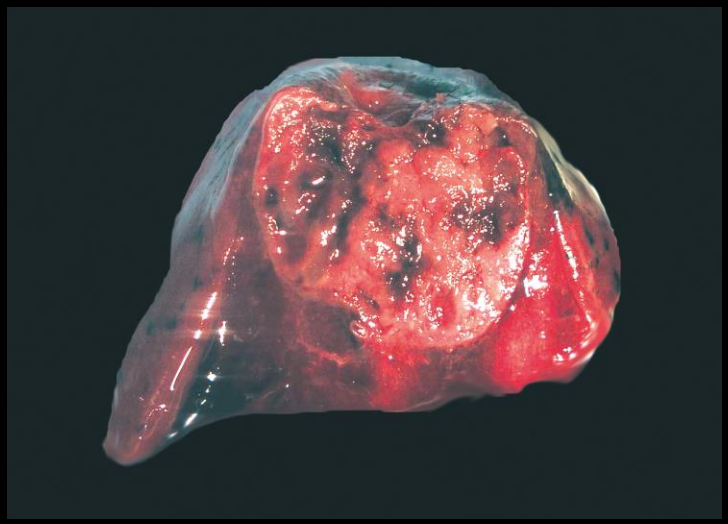
Myomelanocytoma of the Lung

("Sugar Tumor;" "Perivascular Epithelioid Cell Tumor [PEComa];" "Epithelioid Angiomyolipoma")

- Part of a group of tumors that may arise in several organ sites (soft tissue, uterus, gut, lung, kidney, pancreas, etc.) and which show concurrent myogenous and melanocytic differentiation (often with adipocytic elements as well)
- Originally described in lung over 40 yrs ago by Liebow & Castleman
- Usually asymptomatic and found by screening chest radiographs; may occasionally produce cough or hemoptysis; usually seen in adults
- May occur in patients with tuberous sclerosis, who also have micronodular pneumocytic hyperplasia and/or leiomyomatosis of the lung





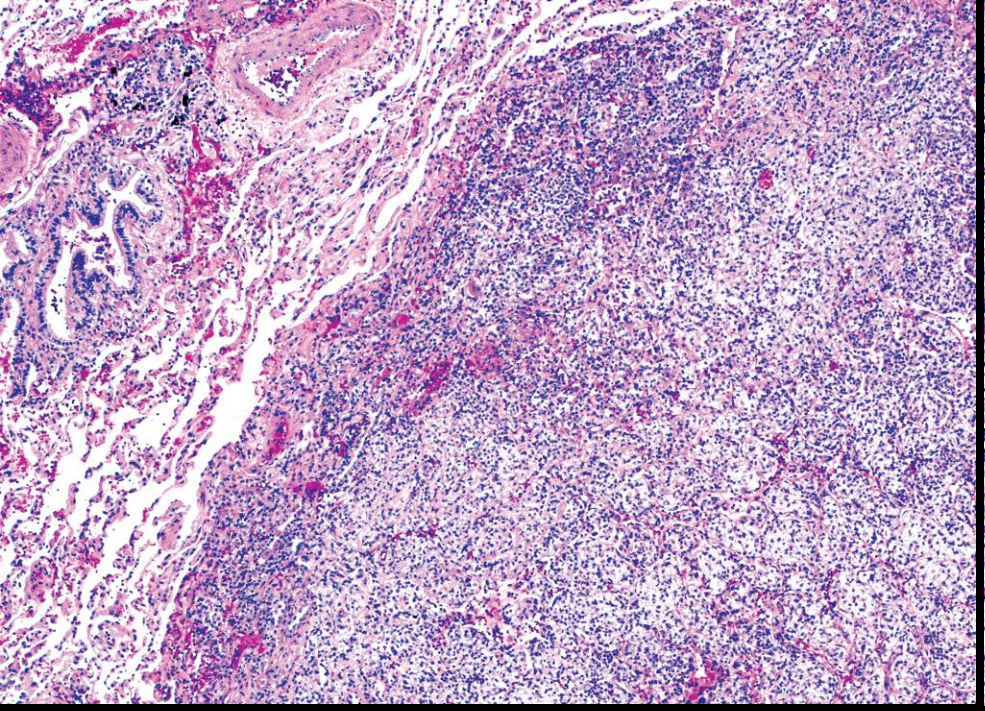
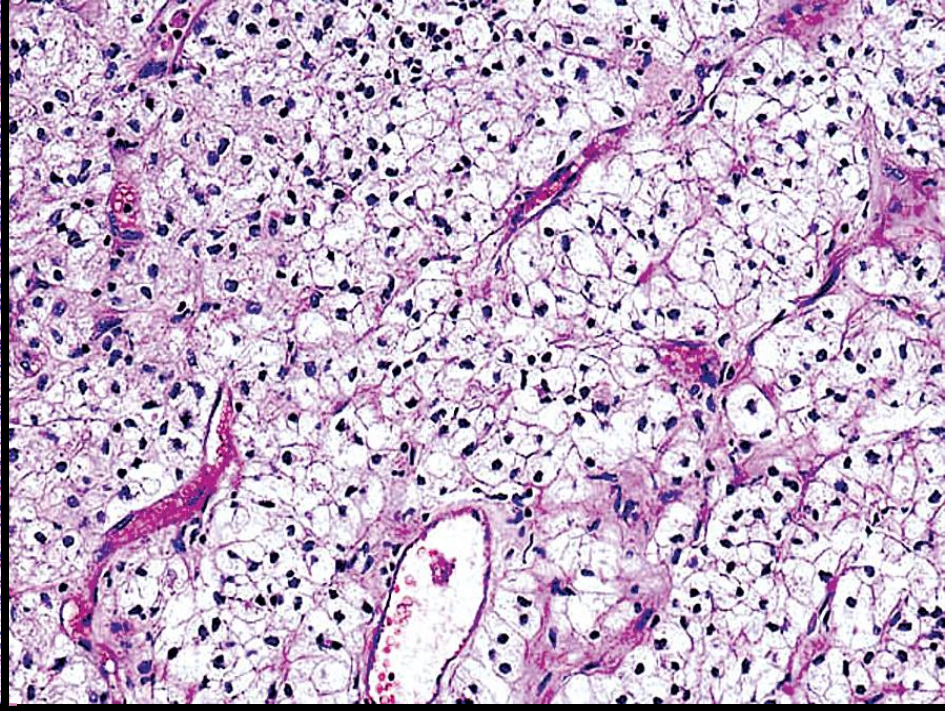
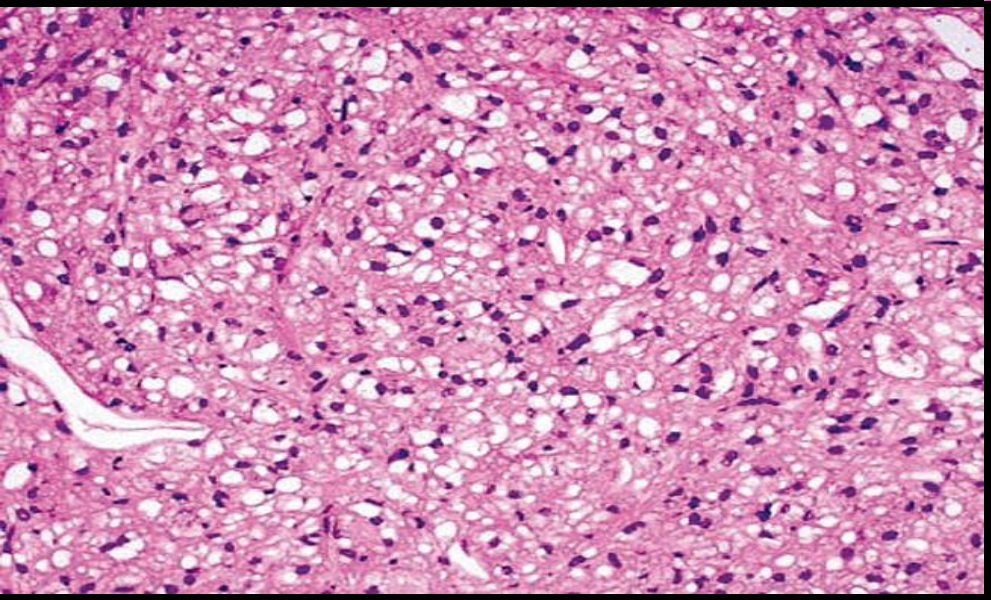
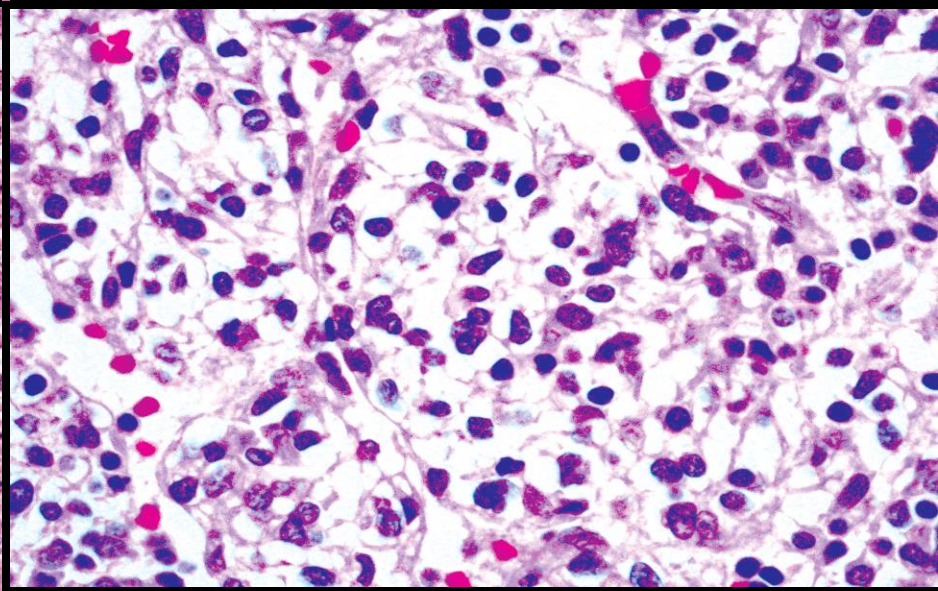


Sugar Tumor of Lung– Radiographic & Gross Images

Myomelanocytoma of the Lung

("Sugar Tumor;" "Perivascular Epithelioid Cell Tumor [PEComa];" "Epithelioid Angiomyolipoma")

- **Variable microscopic appearance; medullary, clustered, or partial spindle-cell growth may be seen**
- **Cytoplasm clear or amphophilic**
- **Modest nuclear atypia and scattered mitotic figures**
- **Usually no necrosis**

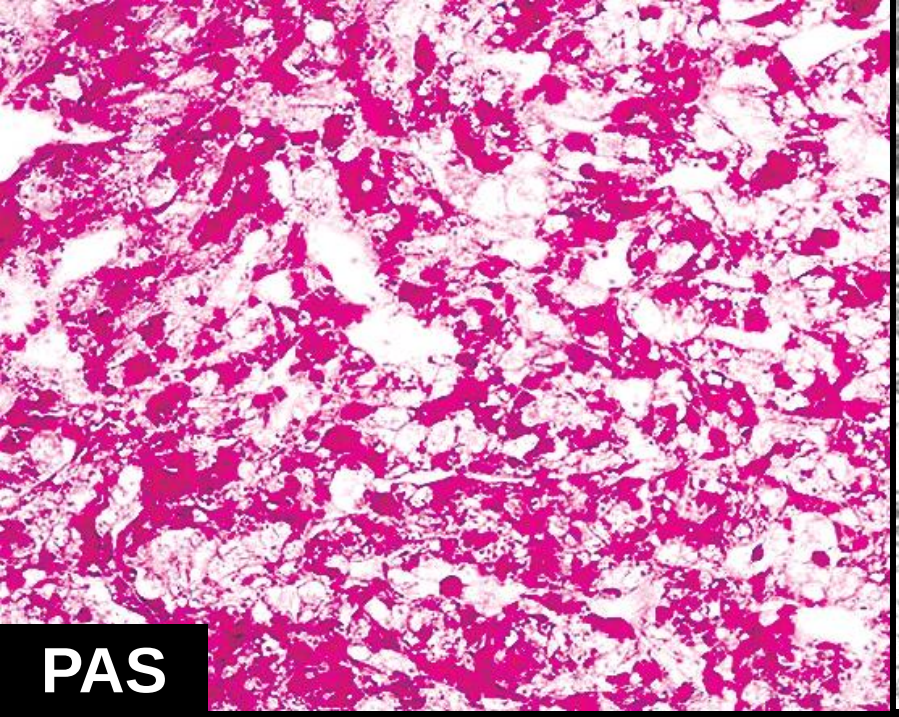





Sugar Tumor of Lung– Microscopic Images

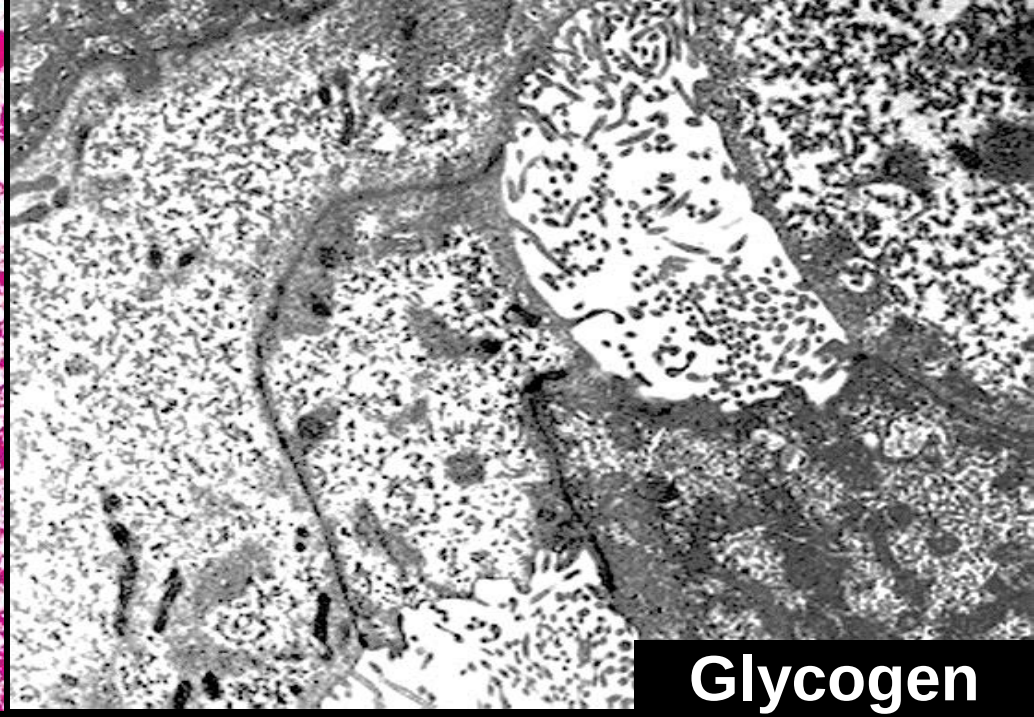
Myomelanocytoma of the Lung

("Sugar Tumor;" "Perivascular Epithelioid Cell Tumor [PEComa];" "Epithelioid Angiomyolipoma")

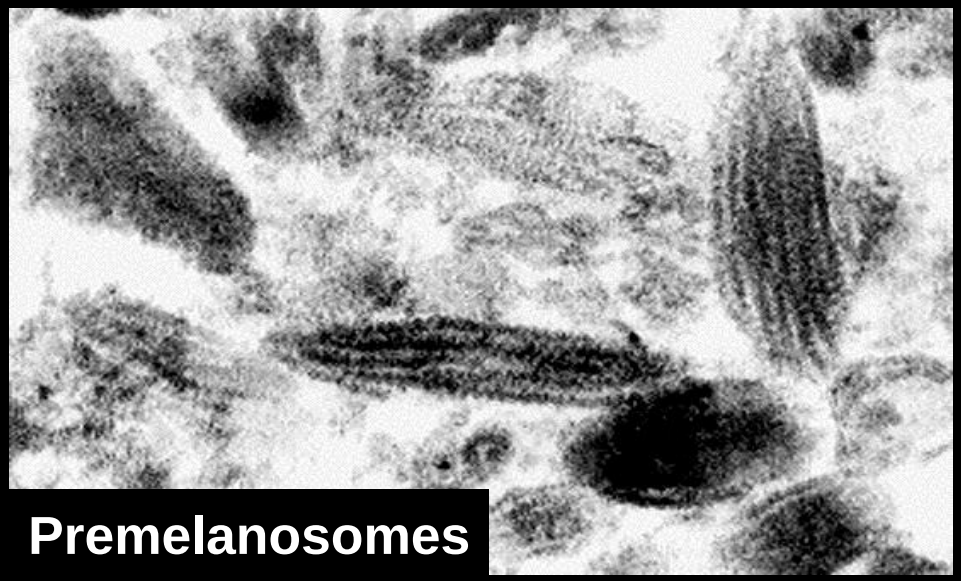
- **Abundant glycogen content with PAS stains**
- **IHC demonstrates keratin-negativity with labeling for HMB-45, melan-A, actins, CD117, & *cytoplasmic* Myo-D1 (a reproducible artifact)**
- **Electron microscopy shows conjoint myogenous and melanocytic differentiation, with premelanosomes**



PAS

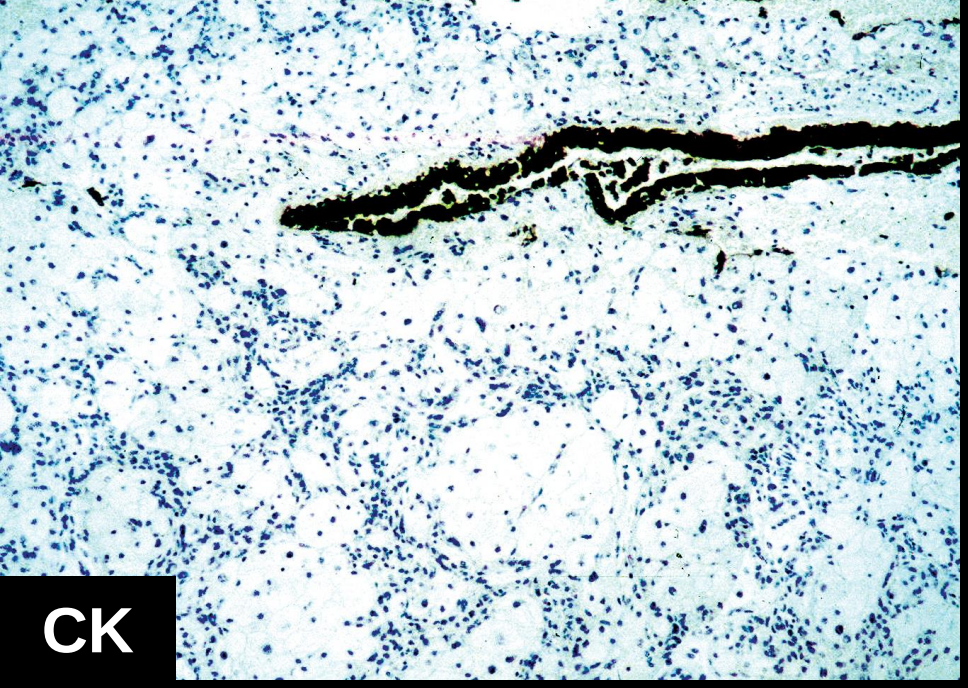


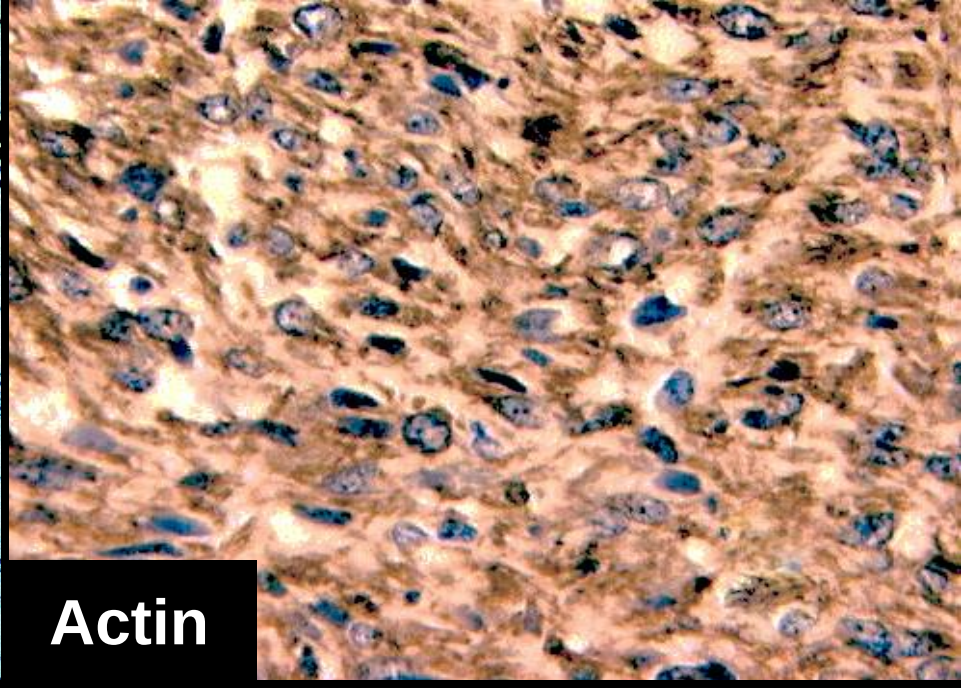
Glycogen

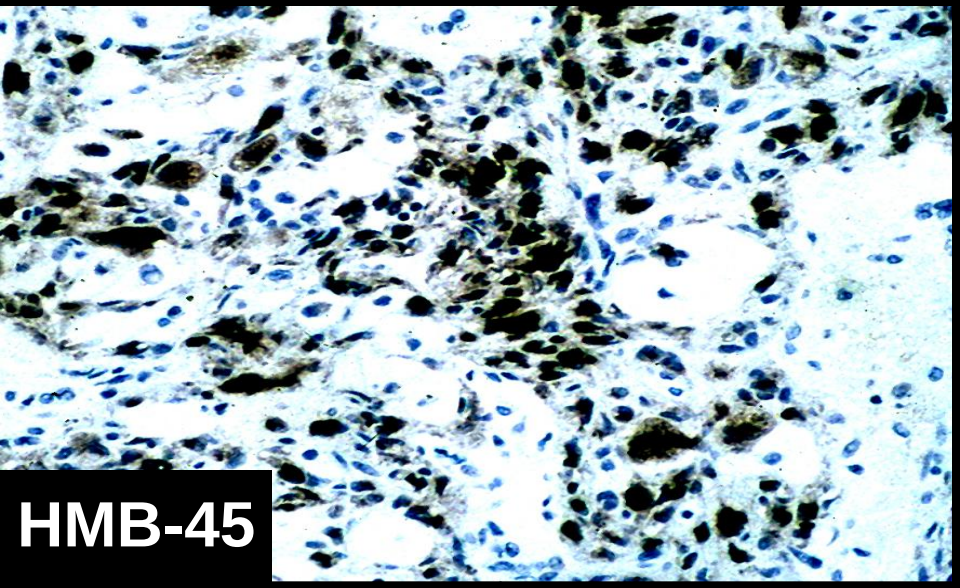


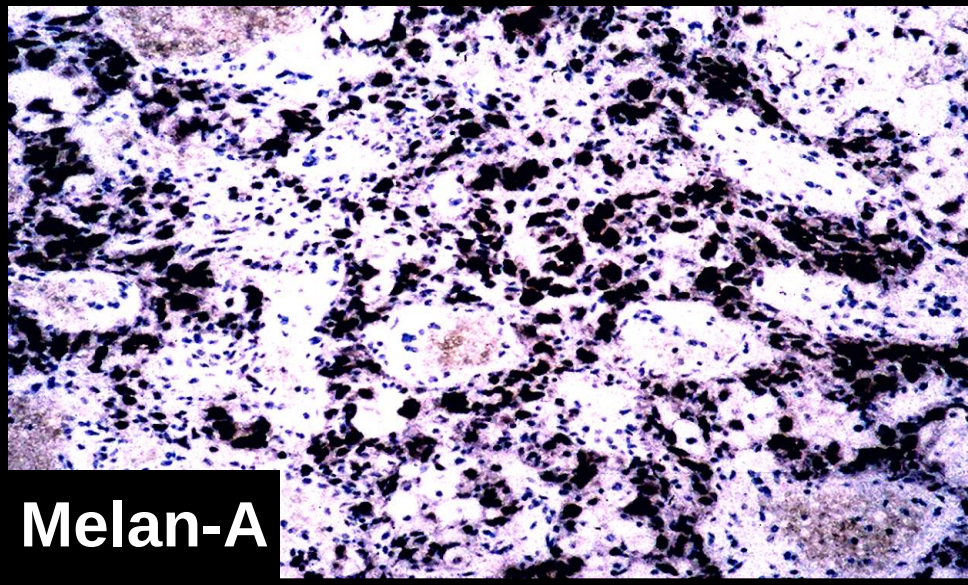
Premelanosomes

Sugar Tumor of Lung– PAS Stain & Ultrastructural Images









Sugar Tumor of Lung– Immunohistochemistry

Myomelanocytoma of the Lung

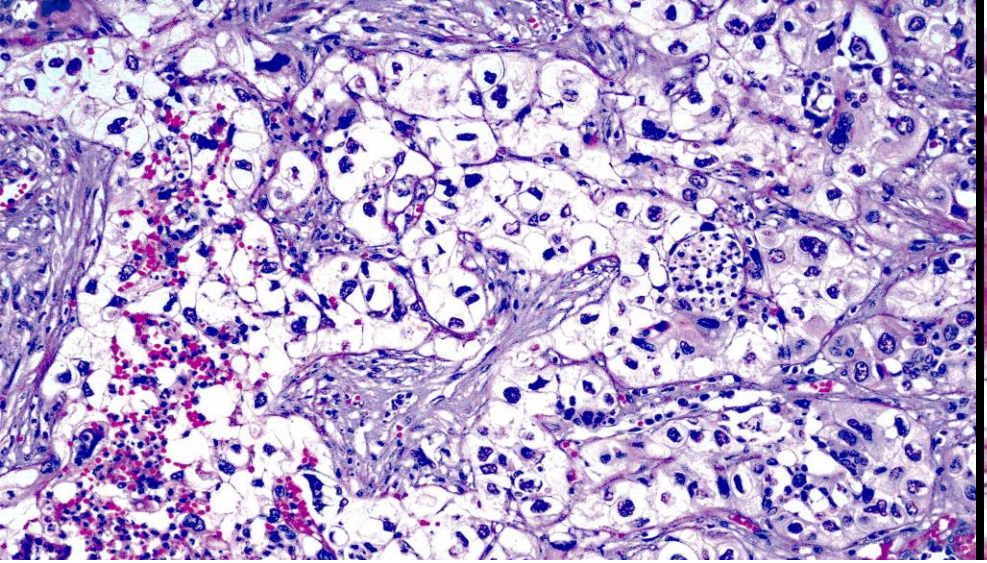
("Sugar Tumor;" "Perivascular Epithelioid Cell Tumor [PEComa];" "Epithelioid Angiomyolipoma")

- Sugar tumor of lung has generally been regarded as benign, but there are at least 2 examples of metastasizing lesions in the literature
- The speaker therefore prefers to place this lesion in the "borderline" category

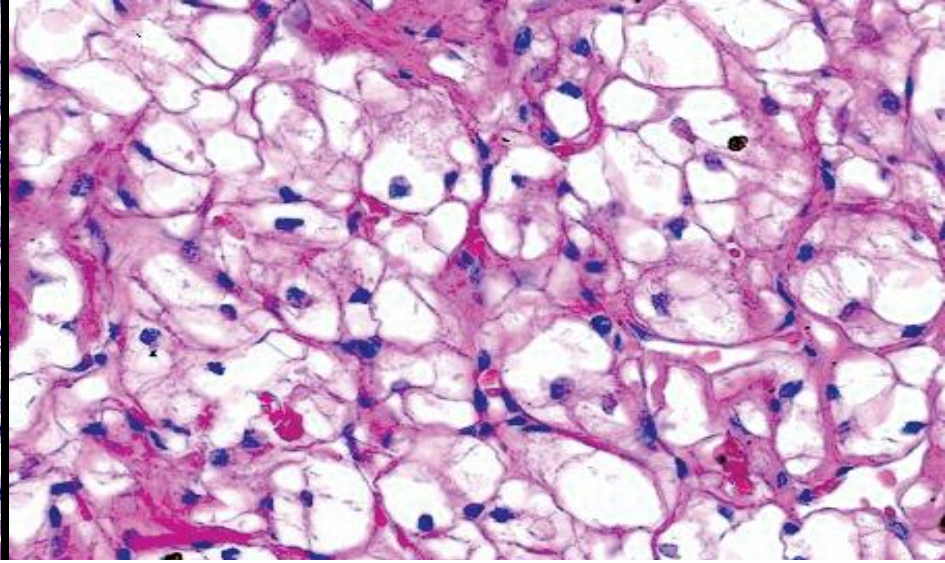
Myomelanocytoma of the Lung

Differential Diagnosis

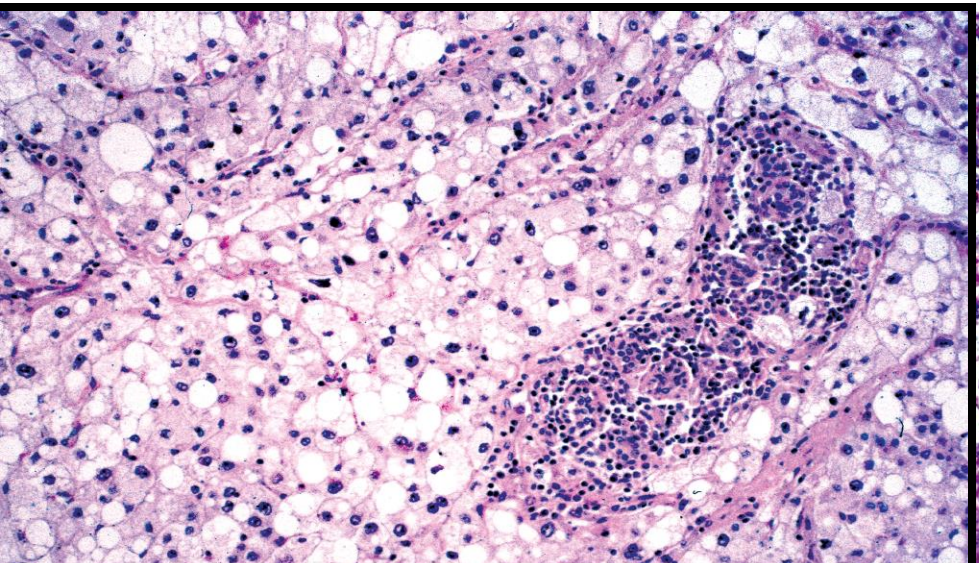
- **Primary or metastatic clear cell carcinoma (keratin +)**
- **Metastatic "balloon-cell" melanoma (Actin- & Myo-D1-negative)**
- **Metastatic clear-cell sarcoma (Actin- & Myo-D1-negative)**



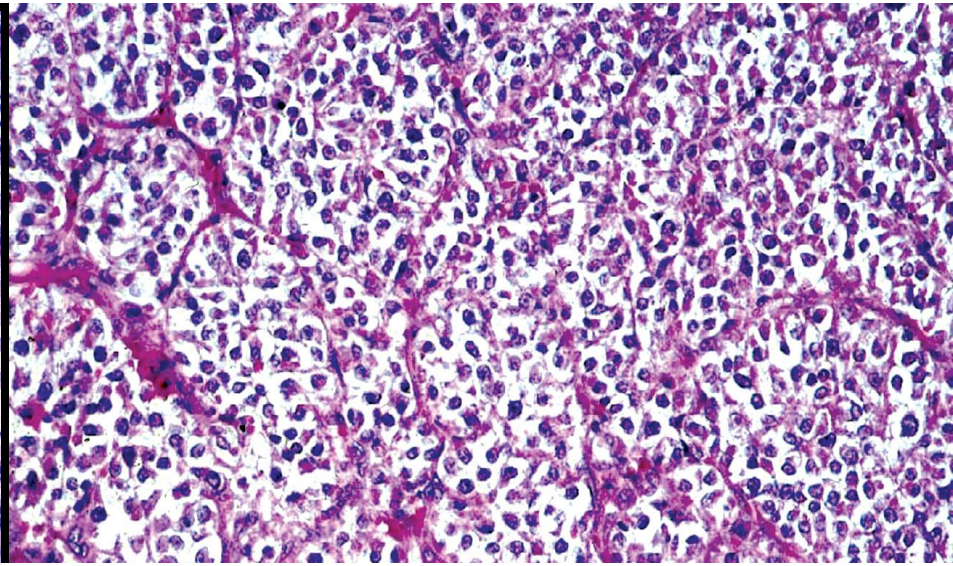
Primary Clear Cell Carcinoma



Metastatic Renal Cell Carcinoma



Metastatic Balloon Cell Melanoma



Metastatic Clear Cell Sarcoma

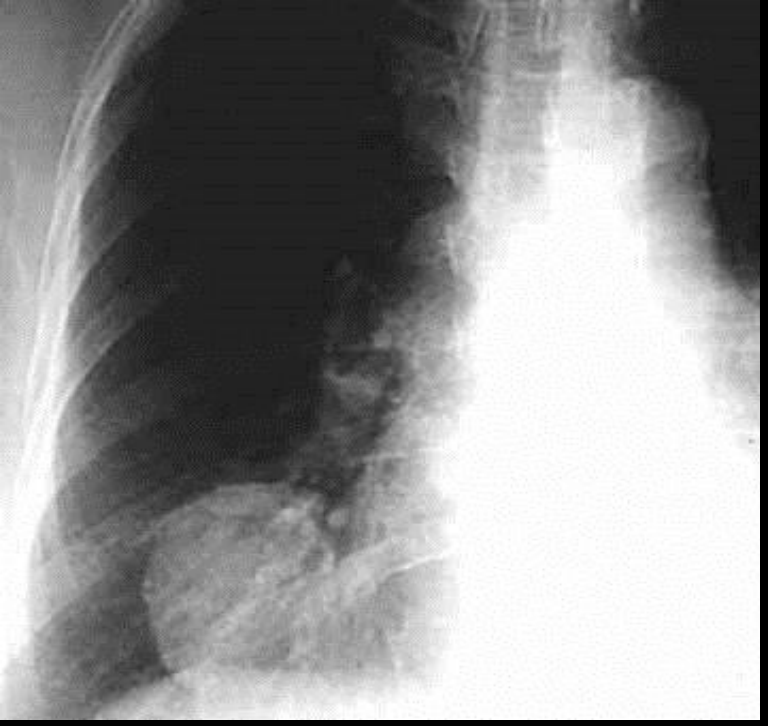
Other Clear Cell Tumors of Lung

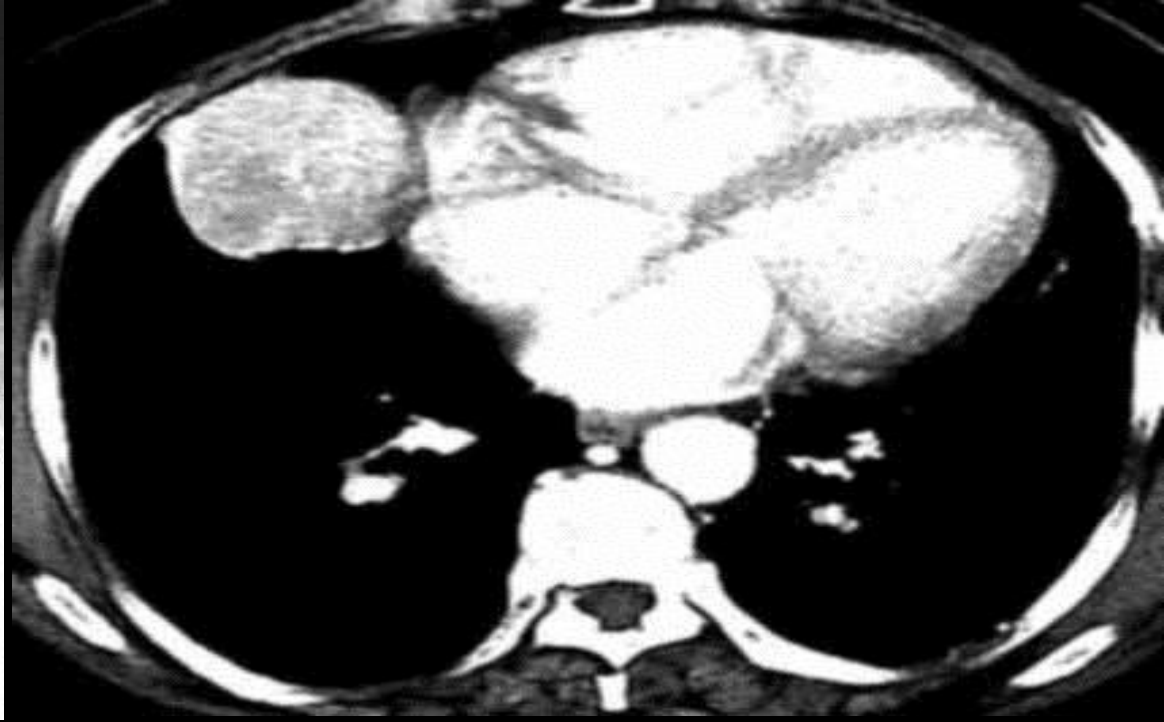
Pneumocytoma
("Sclerosing Hemangioma")

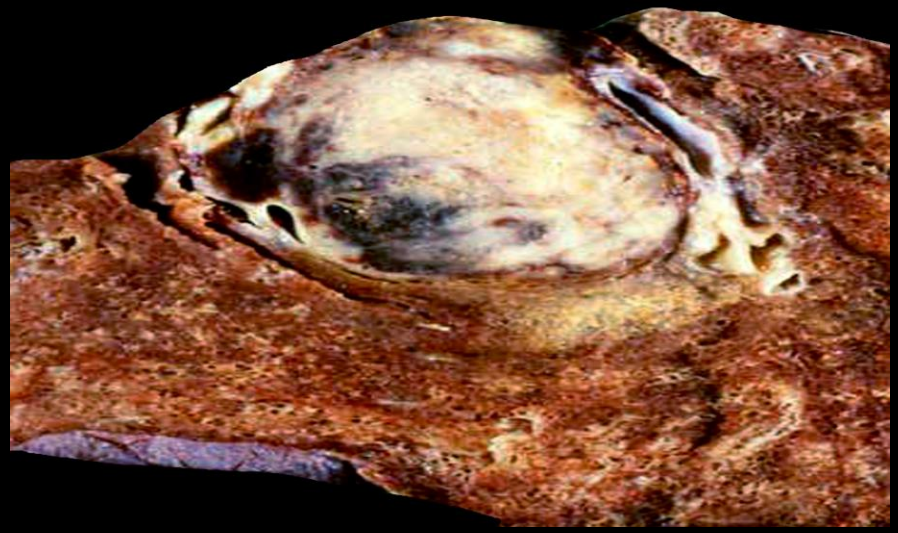
- Described by Liebow & Hubbell 50 years ago
- Name of "sclerosing hemangioma" was chosen in analogy to skin tumors that those authors felt were similar to the pulmonary lesion
- Currently, it is believed that "sclerosing hemangioma" of the lung is actually a proliferation of pneumocytes (types I & II and Clara cells)

Pneumocytoma
("Sclerosing Hemangioma")

- Seen in patients of any age, with females predominating
- One-fifth are symptomatic, with cough, chest pain, or hemoptysis
- Chest films show a circumscribed nodular peripheral lesion measuring up to 10 cm in diameter, sometimes with the "air crescent" sign



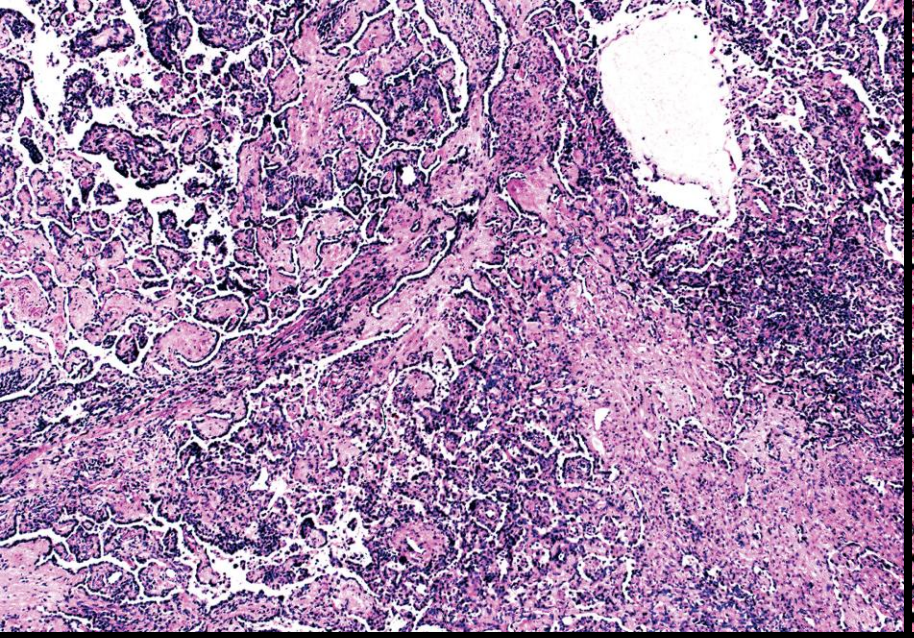


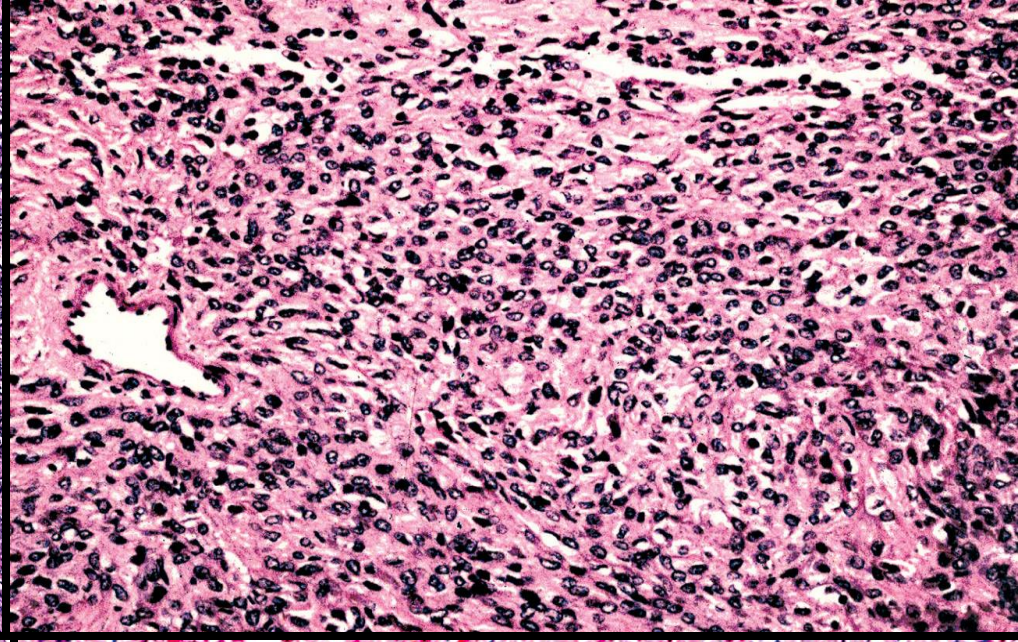


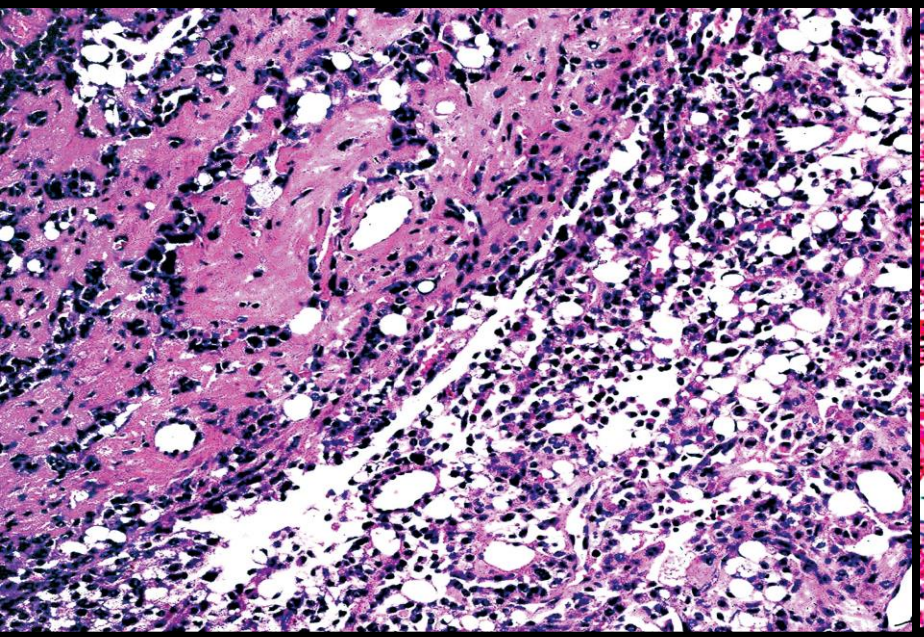
Pneumocytoma– Radiographic & Gross Images

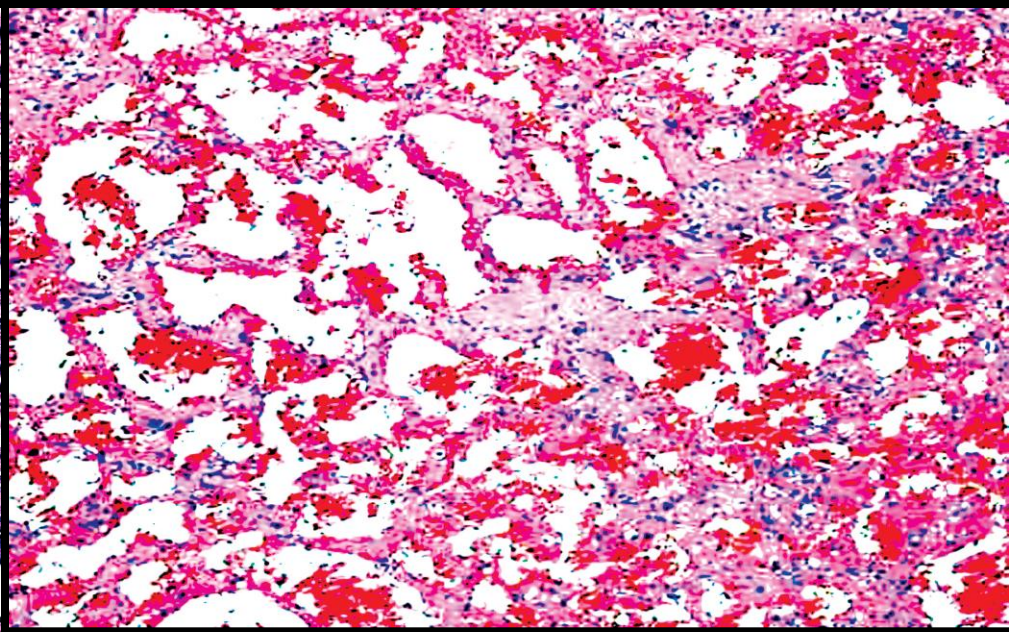
Pneumocytoma
("Sclerosing Hemangioma")

- Two basic cell types– "surface" and "round" cells, which mantle micropapillary arrays & form solid nests, respectively
- Usually-bland nuclear features; mitoses infrequent; cytoplasmic vacuolization; nuclear "pseudoinclusions" as seen in BAC
- 4 basic growth patterns– sclerotic, micropapillary, solid, and angiomatoid
- Secondary features– limited necrosis; calcification; cystification; cholesterolosis; granulomatous inflammation
- *Fine needle aspirates can easily be mistaken for well-differentiated adenocarcinoma*







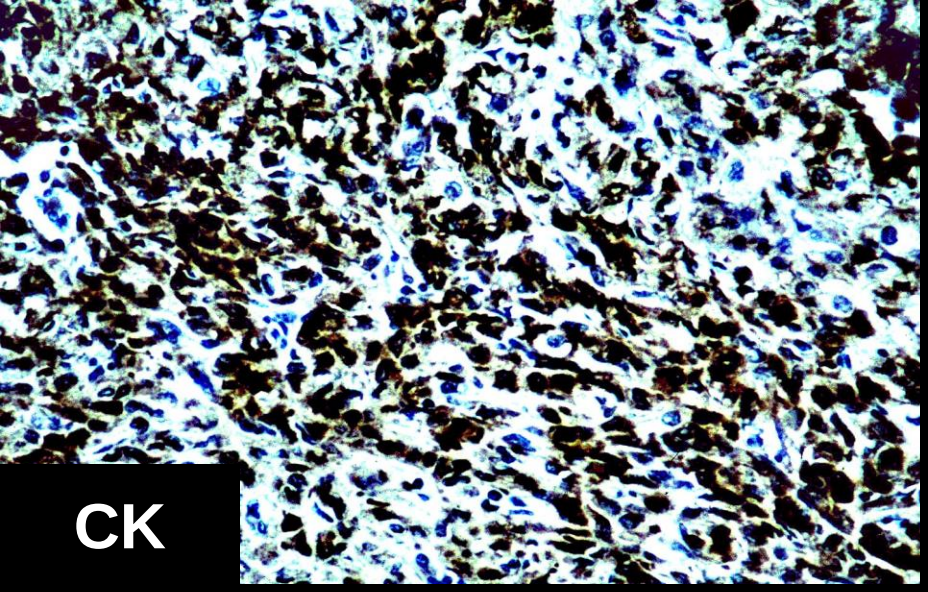


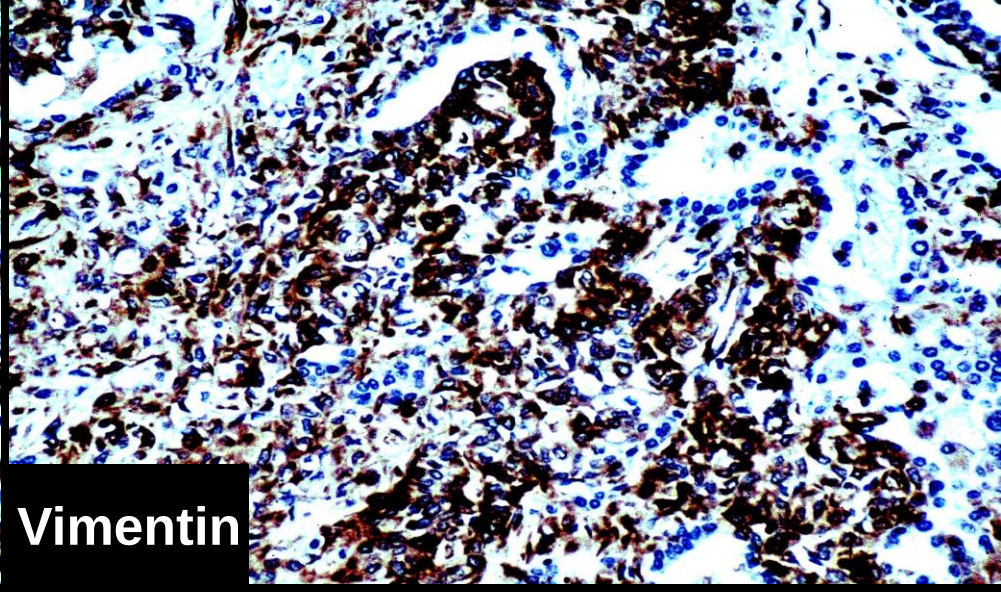
Pneumocytoma– Microscopic Images

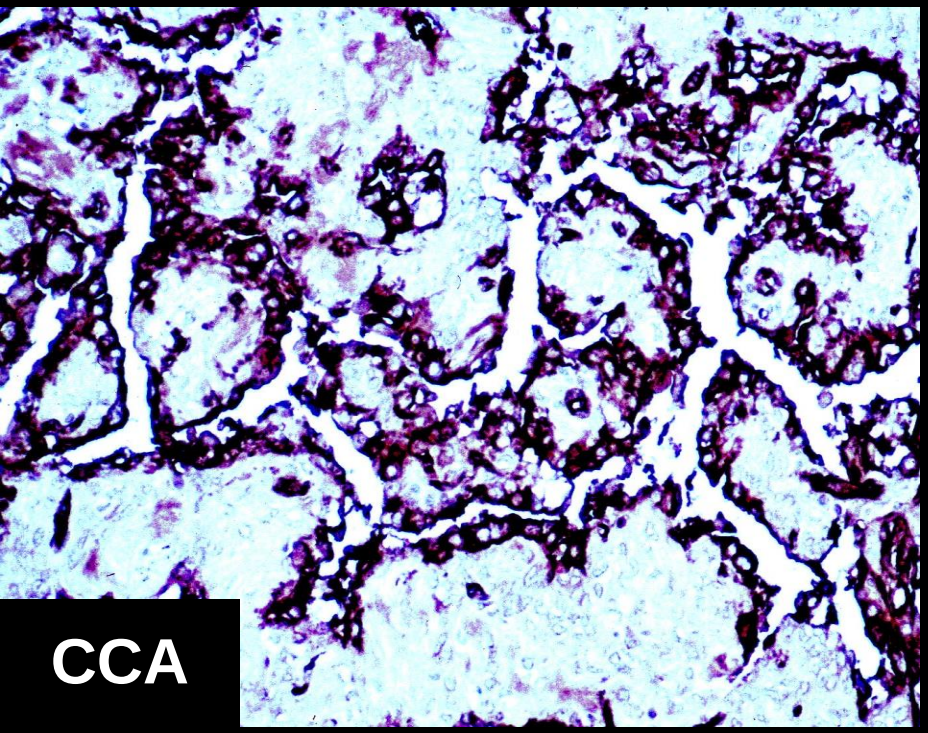
Pneumocytoma

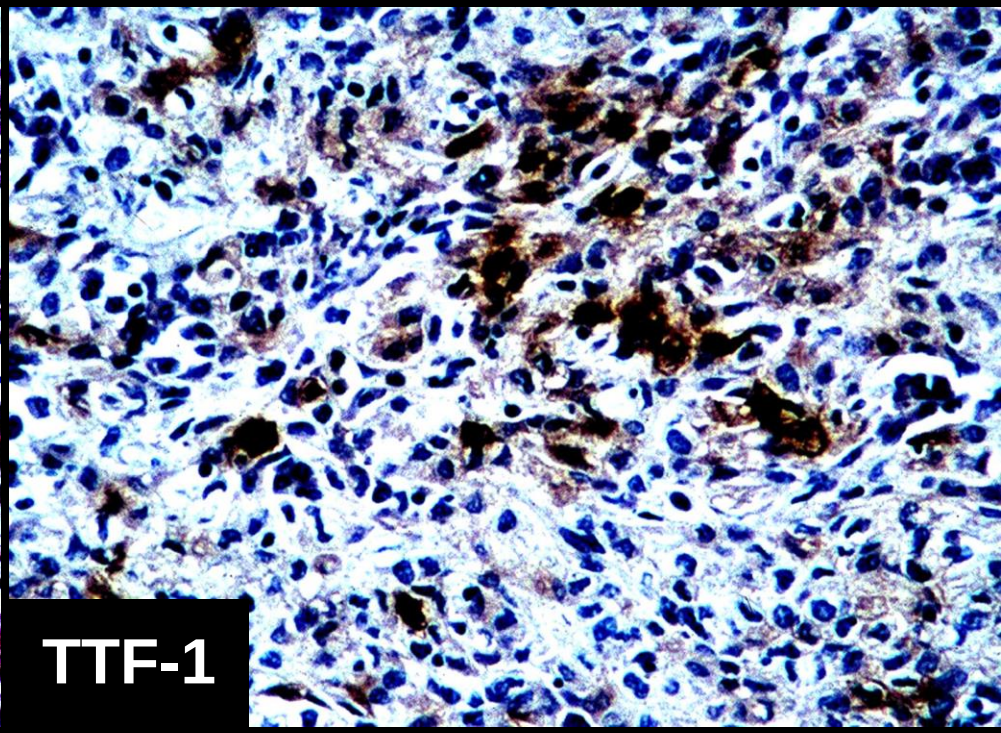
Immunohistochemistry

- **“Surface” cells are uniformly keratin-positive; “round” cells less consistently so**
- **Additional reactivity for vimentin, surfactant-related proteins; Clara-cell antigen; CEA; & thyroid transcription factor-1**









Pneumocytoma– Immunohistochemistry

Pneumocytoma

Behavior

- Several reports have been made of metastasizing pneumocytomas, justifying their classification as "borderline" tumors
- ***However*, metastasis has been limited to regional lymph nodes and does not seem to compromise survival**

Pulmonary Sclerosing Hemangioma With Lymph Node Metastases

Report of 4 Cases

Aya Miyagawa-Hayashino, MD; Henry D. Tazelaar, MD; Desiree J. Langel, MD; Thomas V. Colby, MD

• *Context.*—Sclerosing hemangioma is an unusual pulmonary tumor. Previously, 4 patients with pulmonary sclerosing hemangioma and lymph node metastases have been described in the literature.

Objective.—To report 4 additional cases of metastatic sclerosing hemangioma.

Design.—Retrospective review of the authors' consultation files and review of histologic sections of pulmonary tumors and lymph node metastases.

Results.—Four cases of a morphologically benign pulmonary sclerosing hemangioma with regional lymph node metastases (including hilar, peribronchial, and interlobar metastases) were identified. The patients (3 female, 1 male) had a mean age of 39 years (range, 10–56 years). The tumors ranged in size (greatest dimension) from 1.5 to 4.7 cm (mean, 3.1 cm). The pulmonary tumors were typical circumscribed sclerosing hemangiomas without mitotic activity, angiolymphatic invasion, or necrosis. One tumor had focal cytologic atypia. The metastases were identified in hilar lymph nodes that were removed at operation for the lung nodule. One patient received adjuvant chemotherapy for adenocarcinoma. All of the patients are alive. No recurrences or residual disease has been detected at a mean follow-up of 4.7 years (range, 2.3–10 years).

Conclusions.—On the basis of case data from the 4 patients described here and the 4 patients described previously, metastases to regional lymph nodes from pulmonary sclerosing hemangioma may occur but are rare and do not appear to affect prognosis.

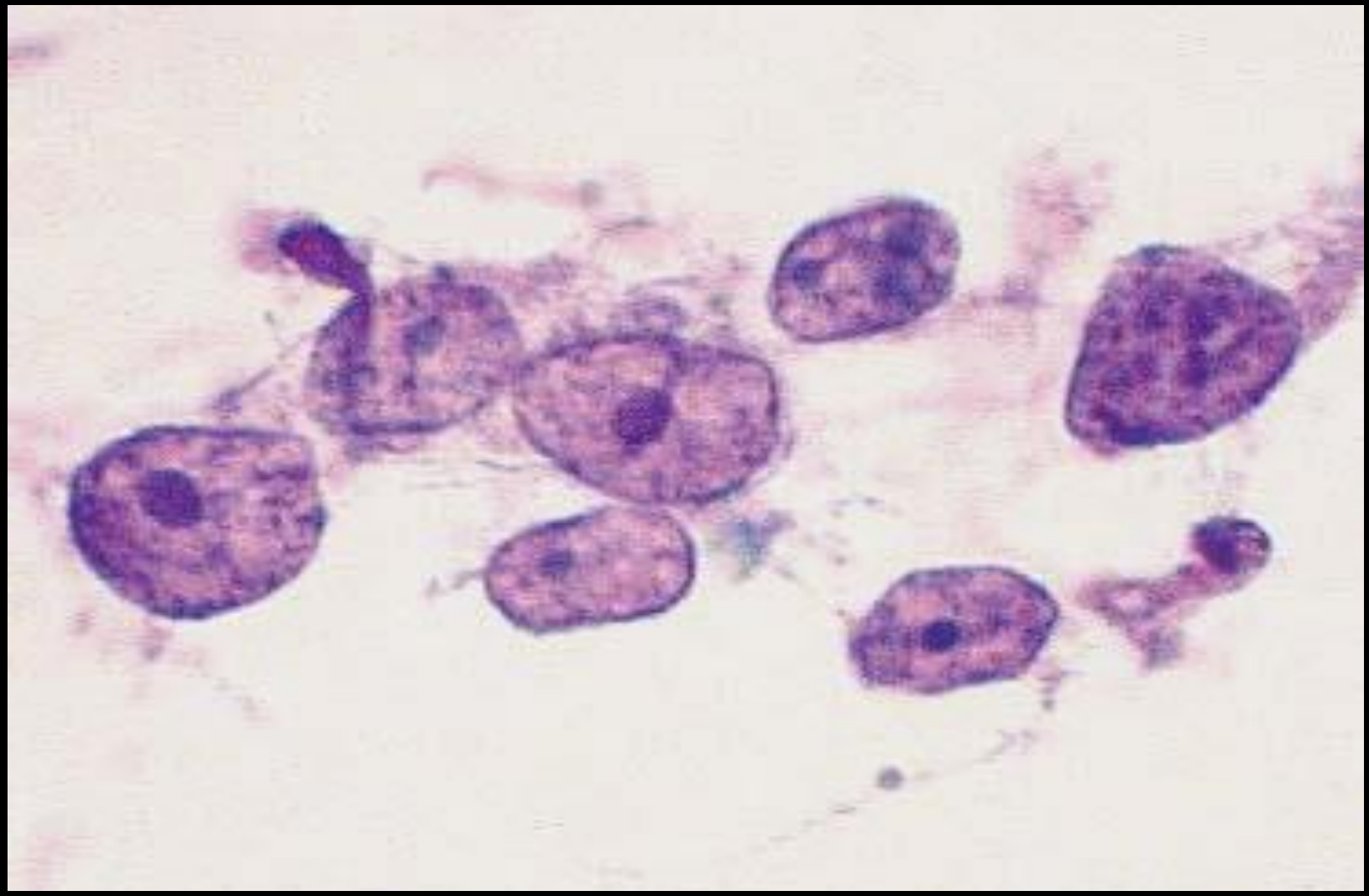
(*Arch Pathol Lab Med.* 2003;127:321–325)

"... metastases to regional lymph nodes from pulmonary sclerosing hemangioma may occur but are rare and do not appear to affect prognosis."

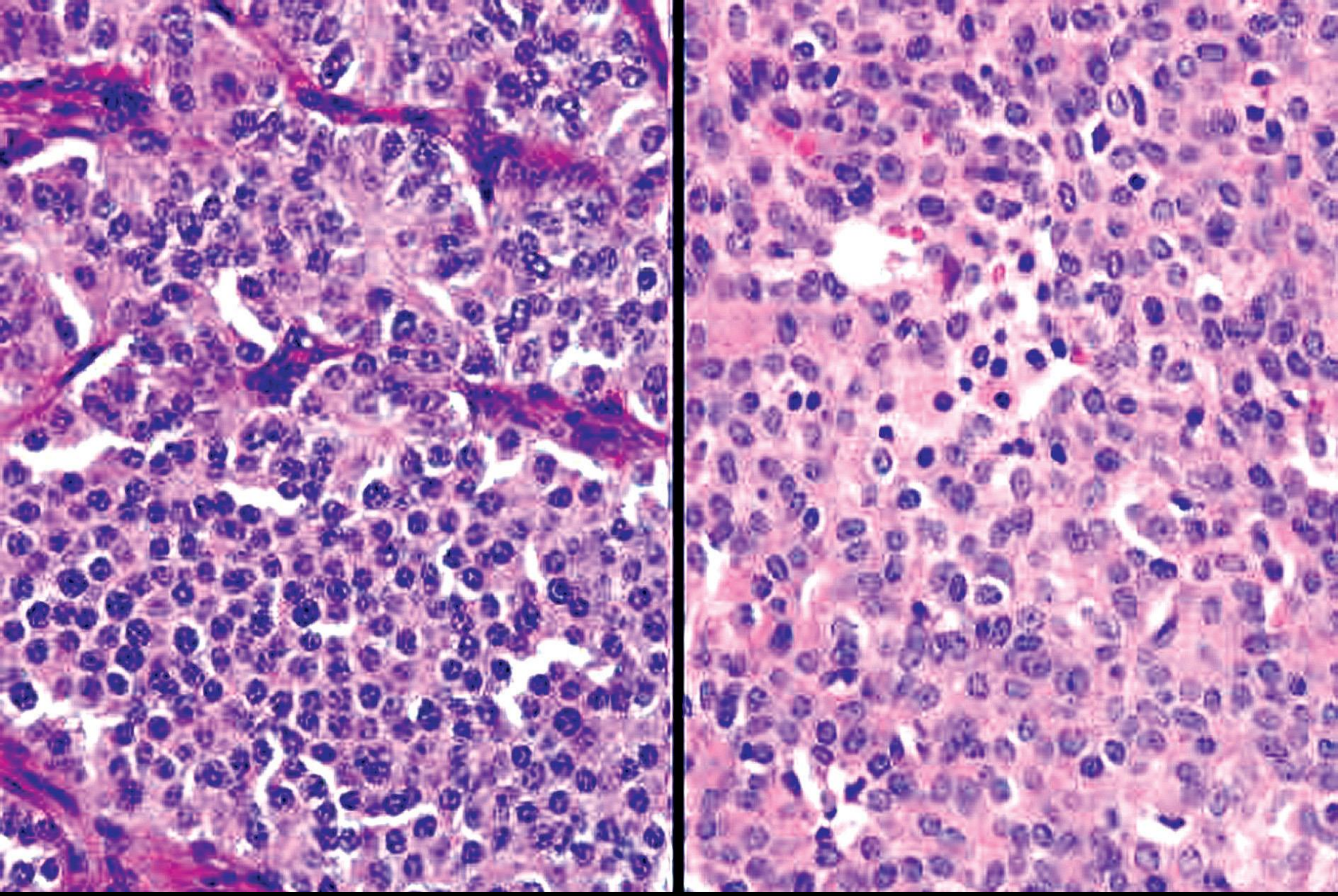
Pneumocytoma

Differential Diagnosis

- **Adenocarcinoma (mainly on FNA)**
- ***"Carcinoid" tumor (Grade I neuroendocrine carcinoma)***



Pneumocytoma– Fine Needle Aspirate



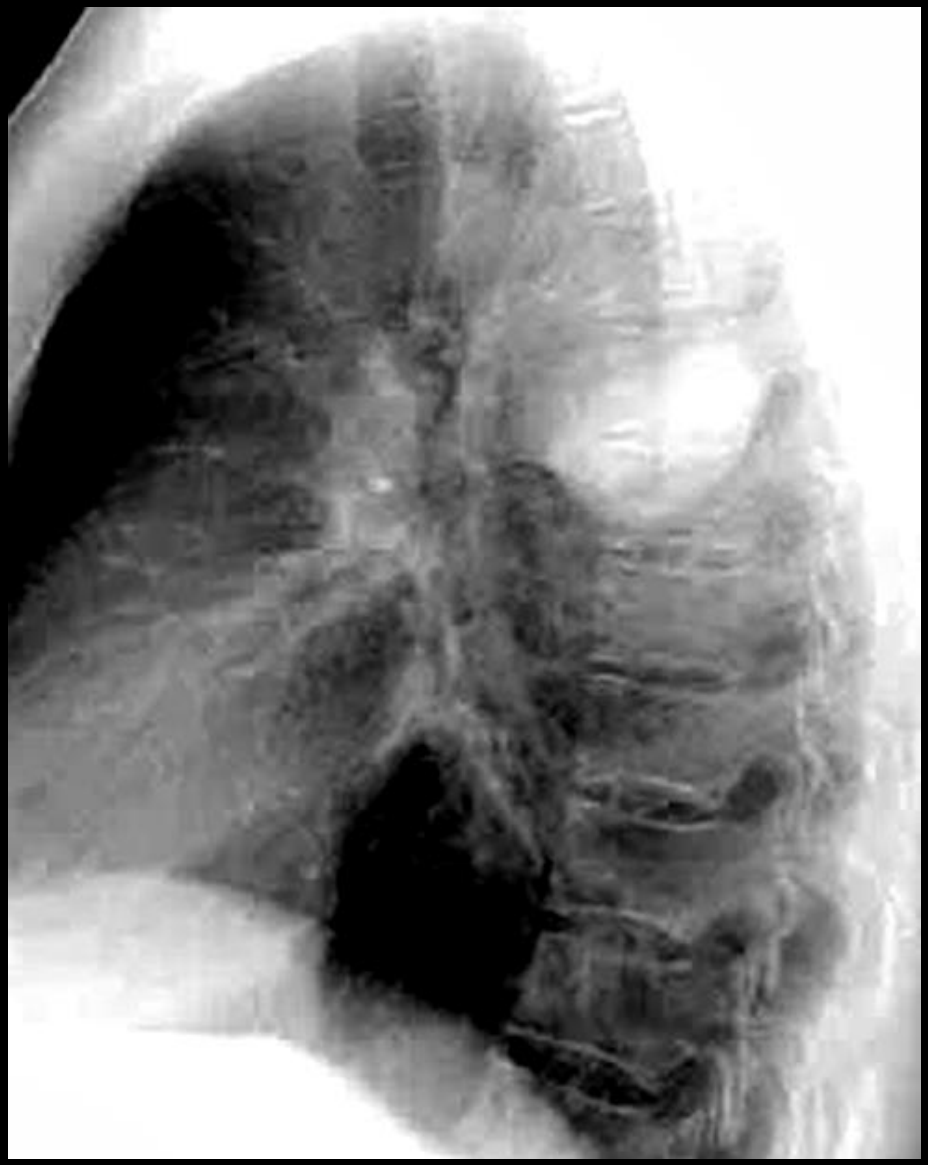
NEC– CGA/CD56+; VIM-

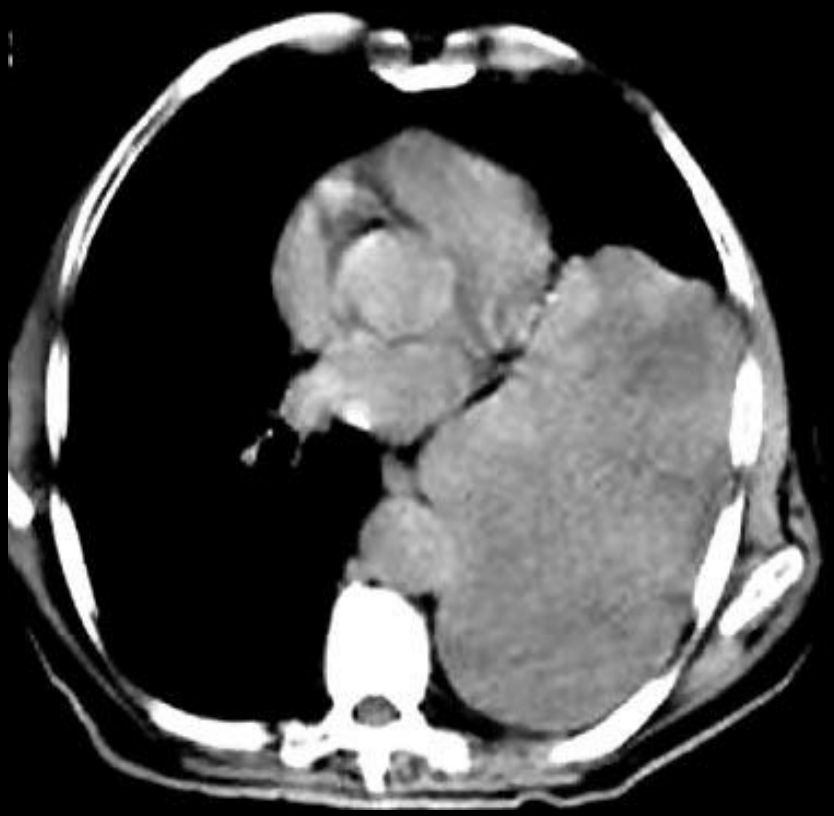
PNEUM– CGA/CD56-; VIM+

Solitary Fibrous Tumor of Pleura

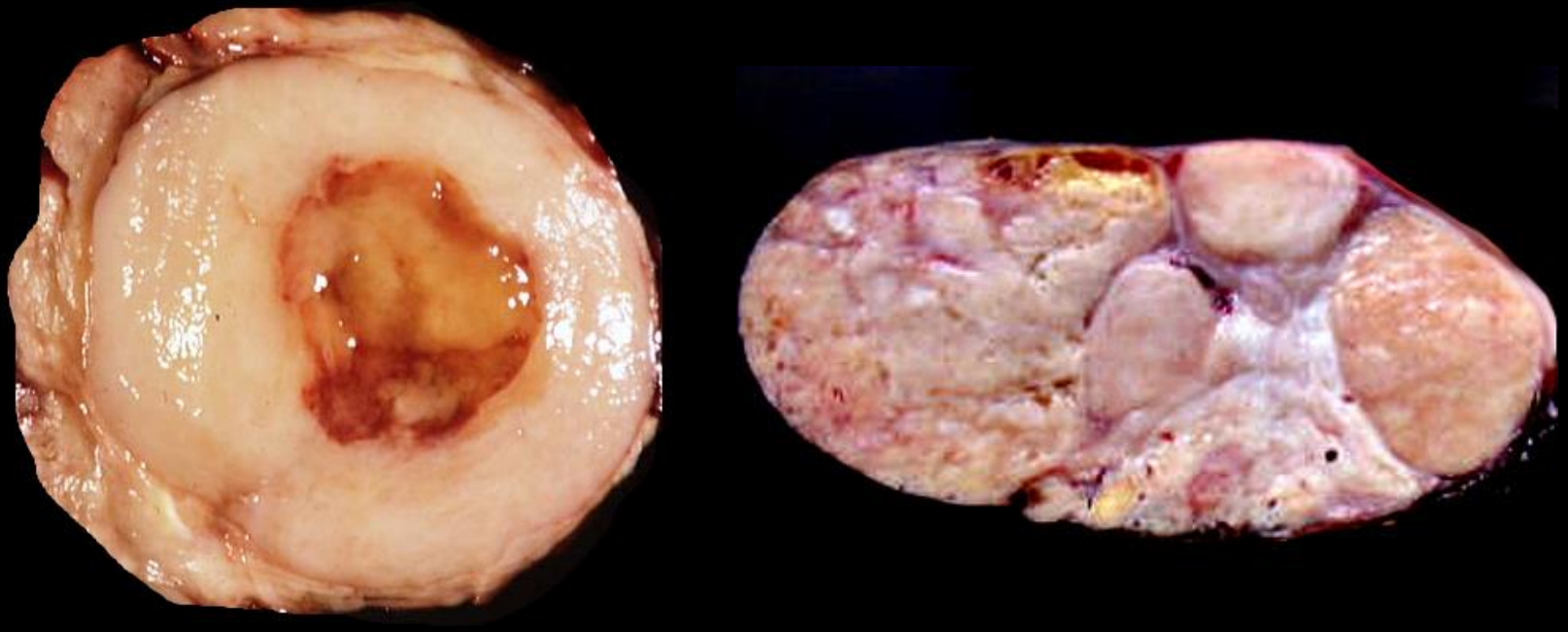
(Pleural Fibroma; "Fibrous Mesothelioma")

- A mesenchymal neoplasm related to hemangiopericytoma, and potentially seen in many anatomic sites
- Still confused with mesothelioma by some clinicians
- Typically seen after age of 40 yrs
- Most are asymptomatic; some cause chest pain, fever, sweats, weight loss, or episodes of hypoglycemia (Potter-Doege syndrome)
- May be huge (up to 35 cm in diameter); usually attached to pleura by a pedicle; may invade chest wall and subjacent lung





Solitary Fibrous Tumor of Pleura– Radiographic Images

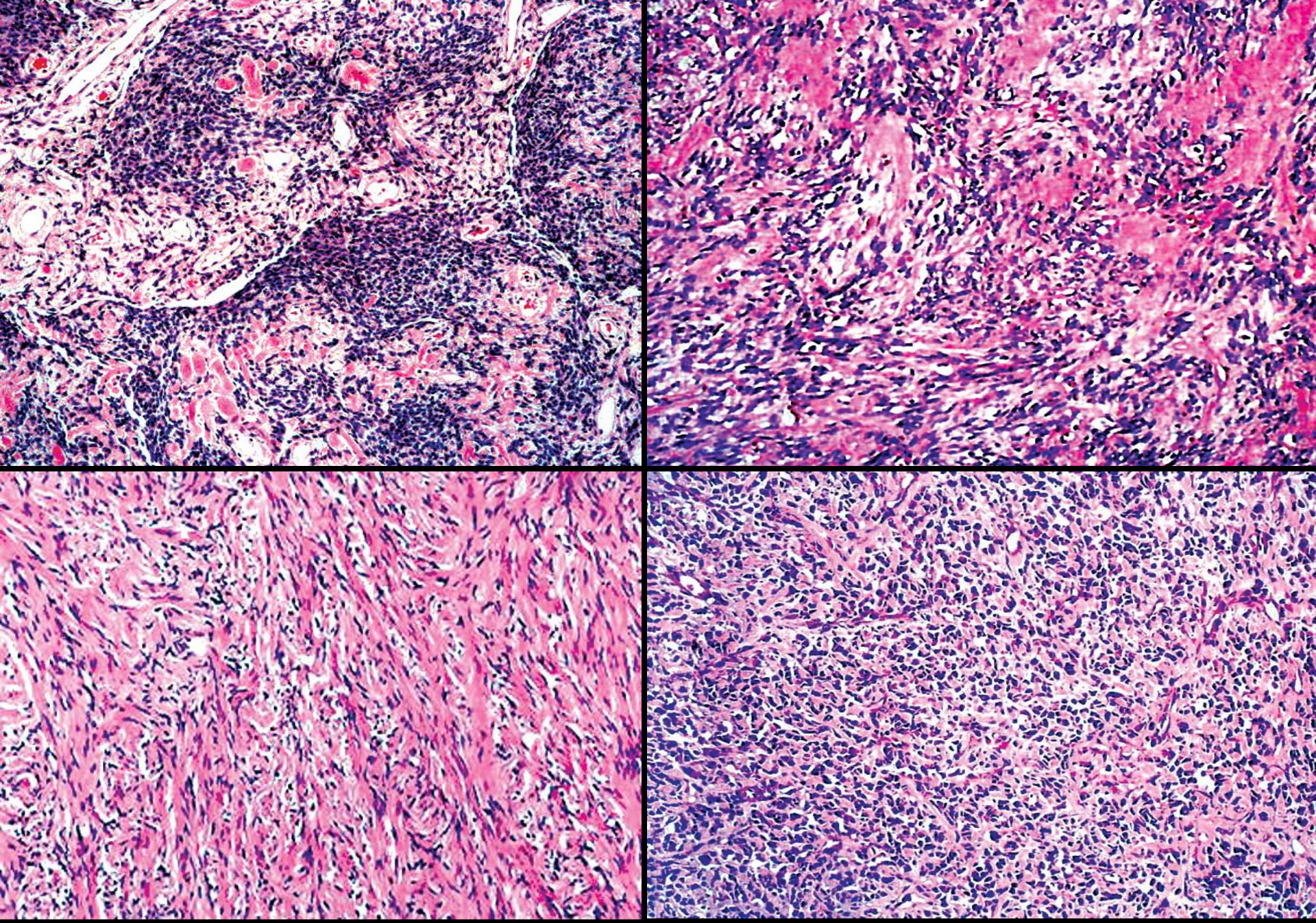


Solitary Fibrous Tumor of Pleura: Gross Images

Solitary Fibrous Tumor of Pleura

(Pleural Fibroma; "Fibrous Mesothelioma")

- **Many potential microscopic appearances– "patternless;" myxoid; sclerotic; palisading; hemangiopericytoid; epithelioid**
- **Mitoses easily found but not usually atypical**
- **Small foci of necrosis may be present, or metaplastic bone**



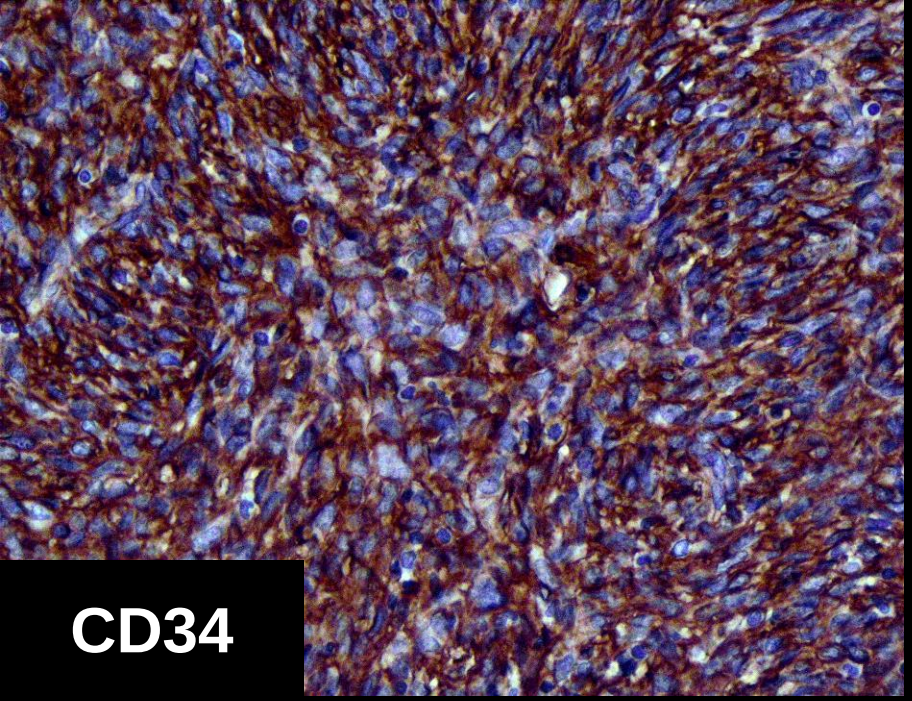
Solitary Fibrous Tumor of Pleura– Microscopic Images

Solitary Fibrous Tumor of Pleura

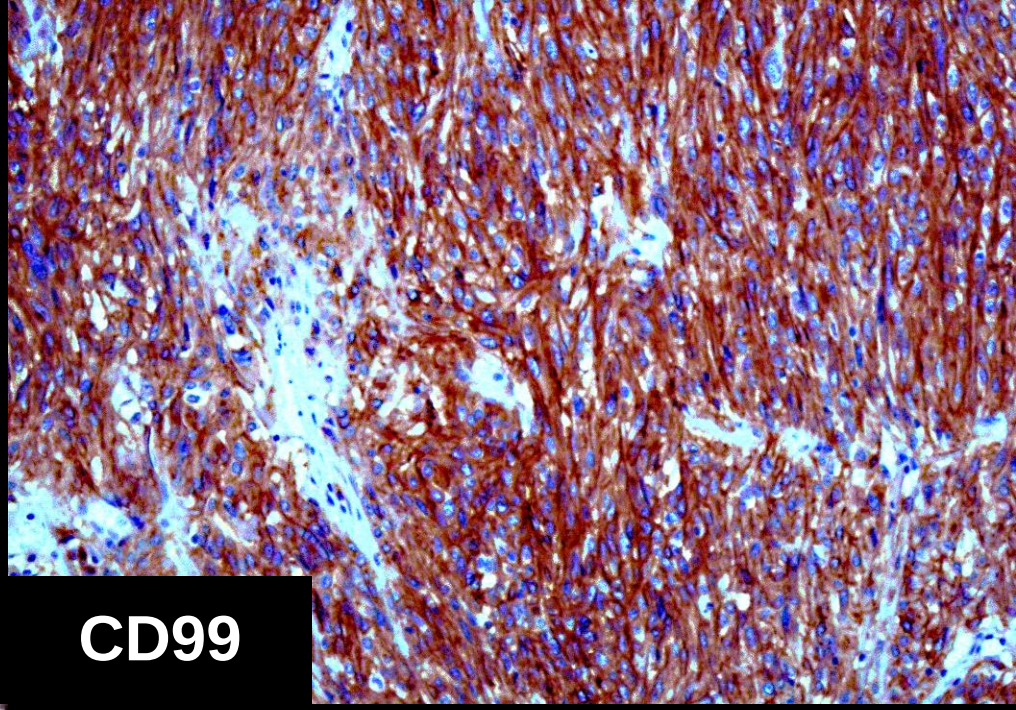
(Pleural Fibroma; "Fibrous Mesothelioma")

- **Immunohistochemistry—**
  - **Vimentin+**
  - **CD34+ (in 85%)**
  - **CD99+ (~75%)**
  - ***Bcl*-2+ (~80%)**
  - ***NEGATIVE* for keratin, EMA, S100 protein, desmin, CD57, & calretinin**

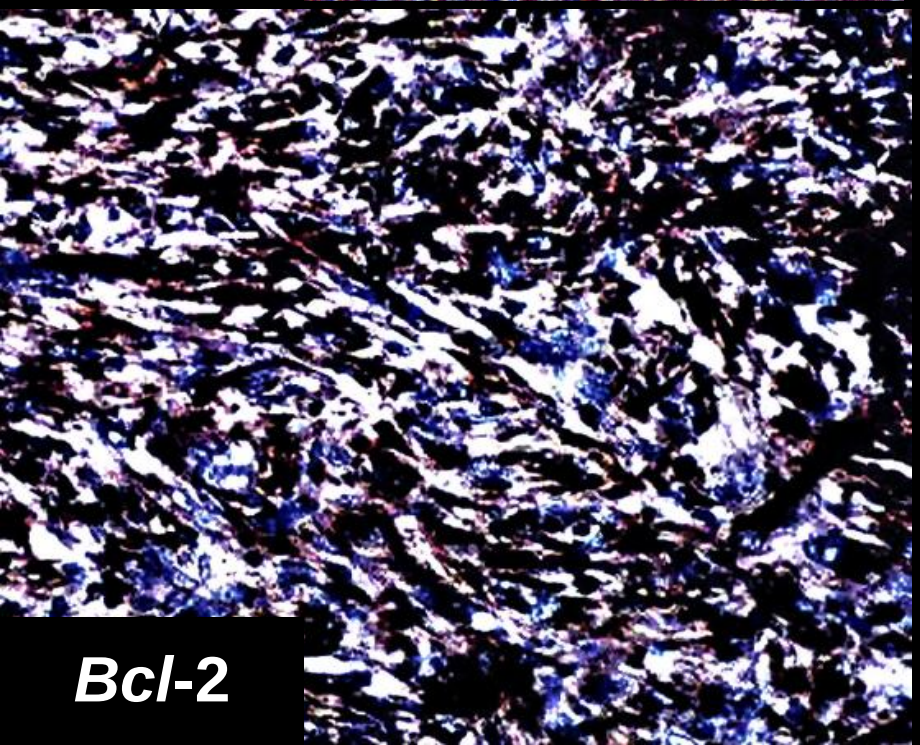
***** Lacks t(X;18) translocation of synovial sarcoma***



CD34



CD99



Bcl-2

Solitary Fibrous Tumor of Pleura: Immunohistology

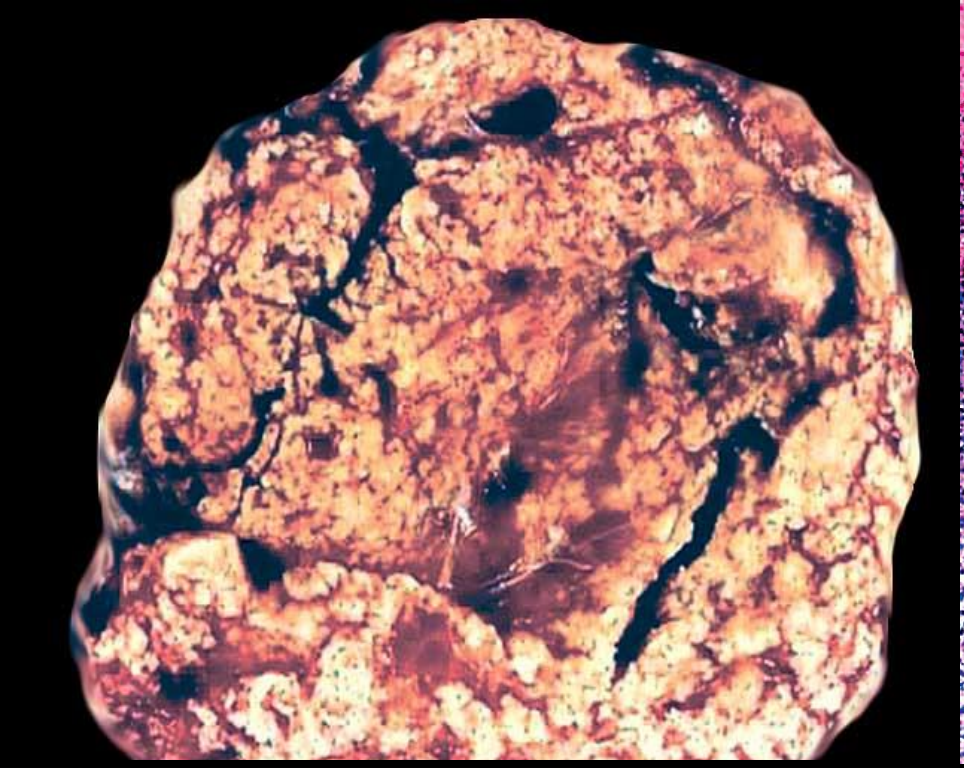
Solitary Fibrous Tumor of Pleura

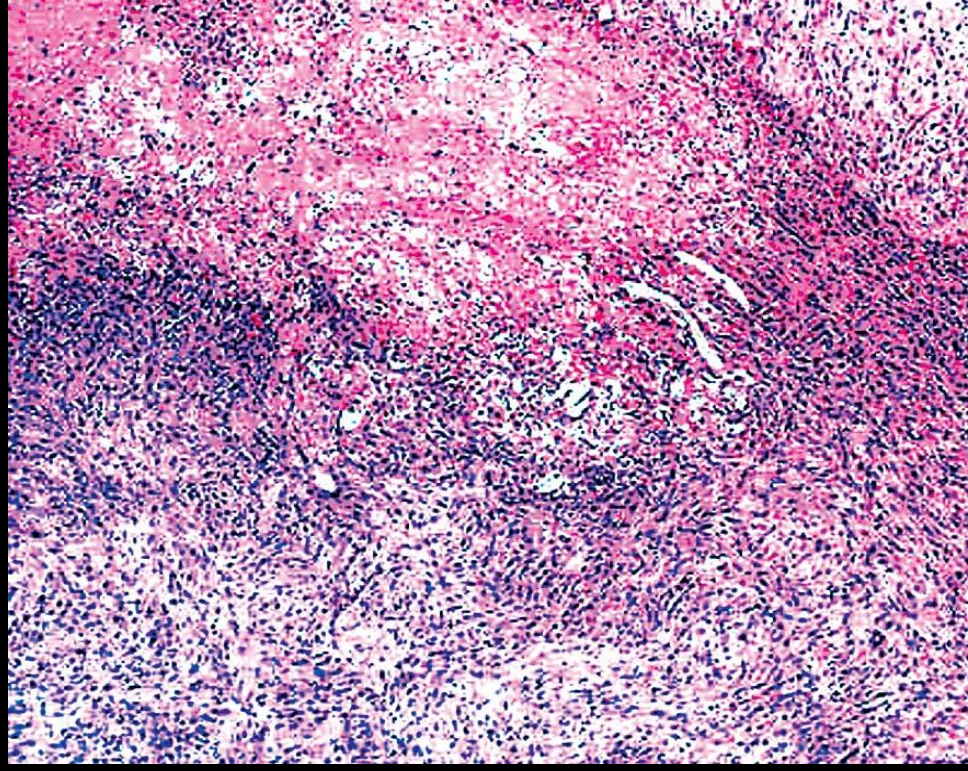
Biology

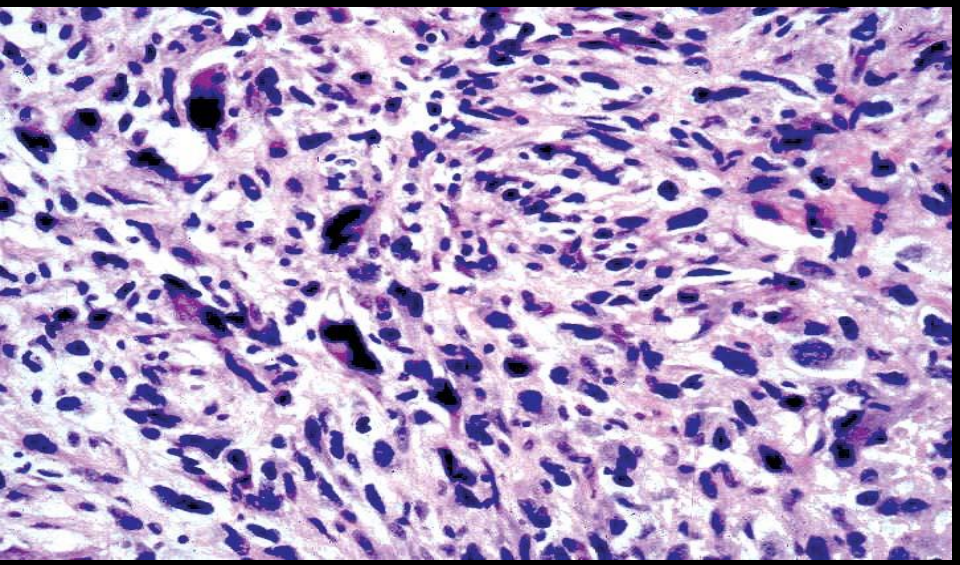
- **SFT may recur and behave aggressively locally; only very rare metastasis of histologically-typical cases**
- **Best never to use the term "benign" in connection with this tumor diagnostically**

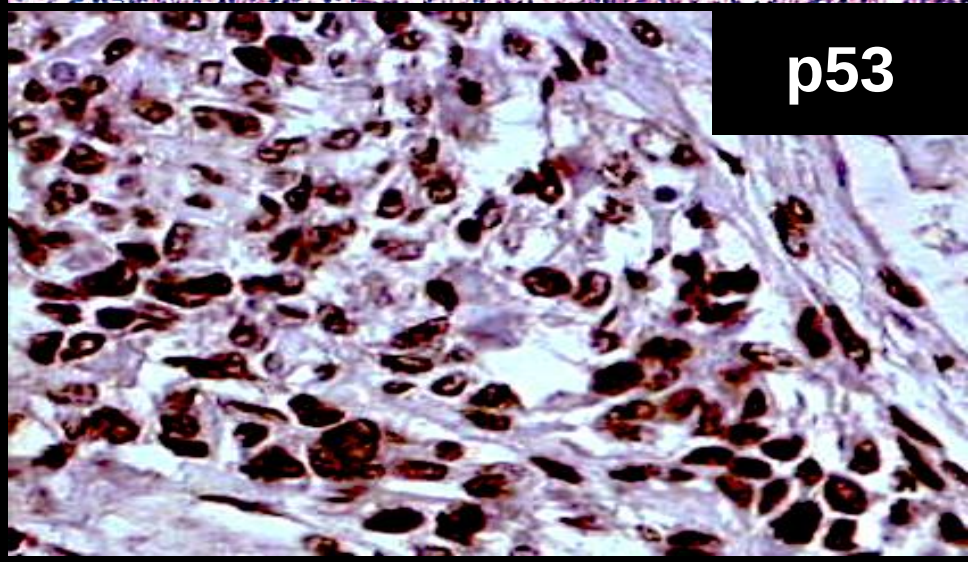
Solitary Fibrous Tumor of Pleura:
Criteria for Outright Malignancy

- **Still in evolution– England et al. suggested that tumors with *dense cellularity & overlapping nuclei; ≥ 4 mitoses per 10 HPF; zonal necrosis; and nuclear anaplasia* should probably be considered malignant SFTs**
- **Diffuse immunoreactivity for mutant p53 protein has also been claimed to correlate with malignancy**





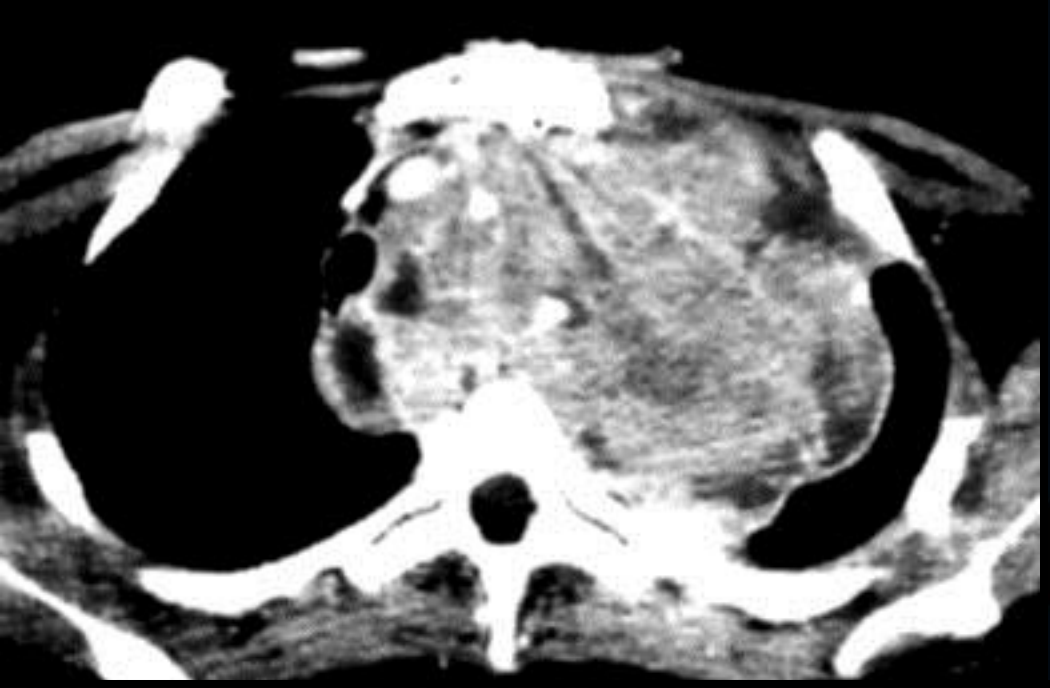


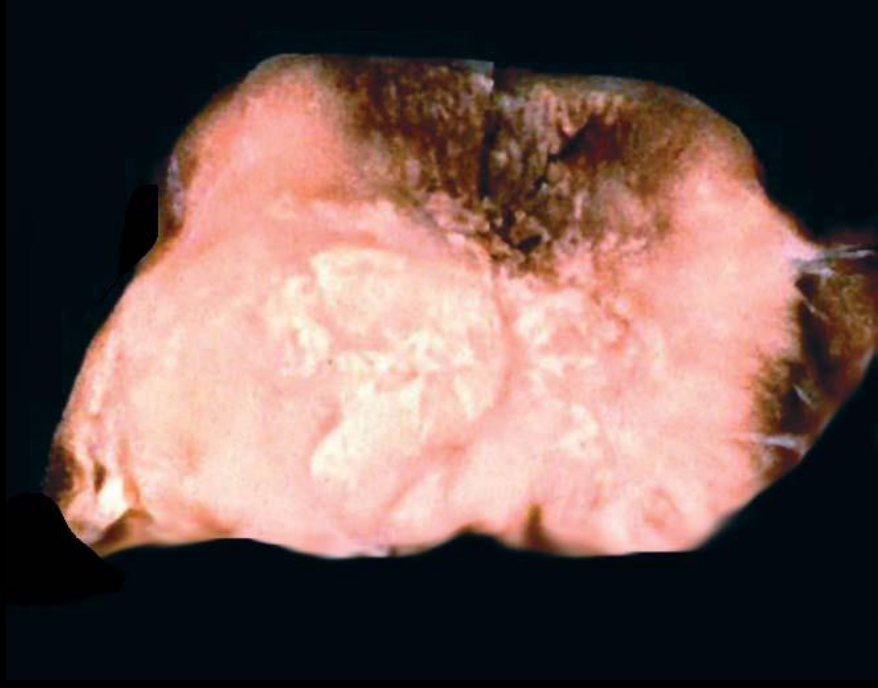


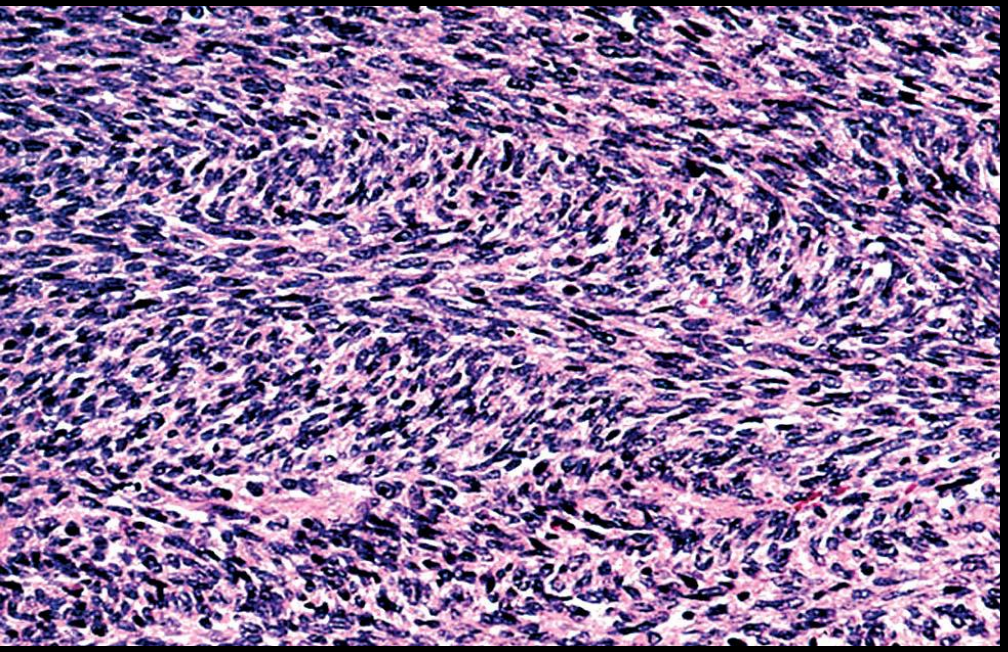
“Malignant” Solitary Fibrous Tumor of Pleura

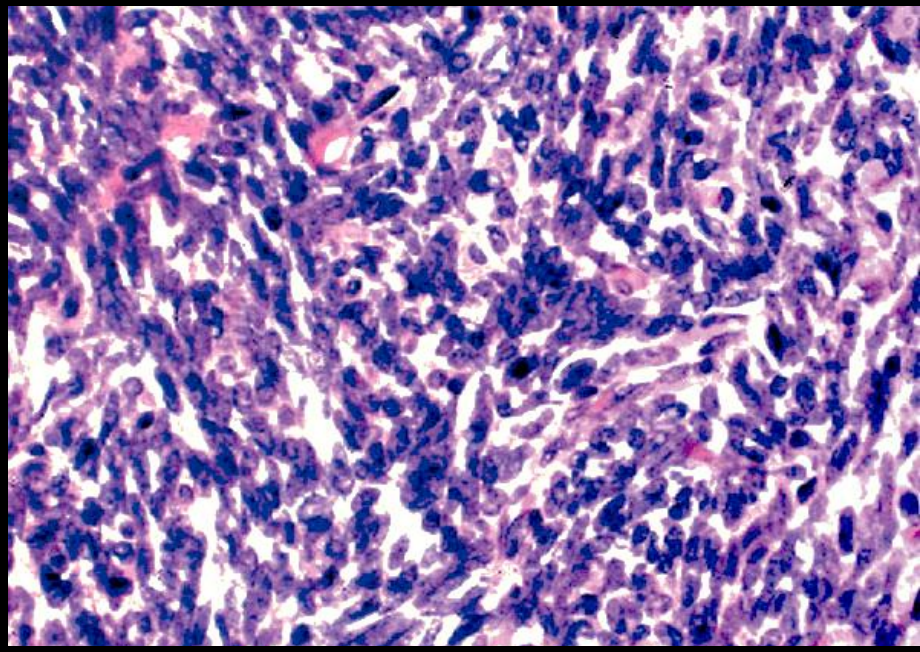
Solitary Fibrous Tumor of Pleura:
Differential Diagnosis

- ***Synovial sarcoma of pleura*–** difficult DDx because of shared immunoreactivity for CD99 & *bcl-2*; however, synovial sarcoma is reactive for EMA, unlike SFT, and shows t(X;18) by FISH
- **Other pleural sarcomas**









Pleuropulmonary Synovial Sarcoma

Other Benign & Borderline Pleuropulmonary Tumors

- ***Benign*– Solitary papilloma & papillomatosis; Neurofibroma; Neurilemmoma; Granular cell tumor; Leiomyoma; Glomus tumor & glomangioma; Chondroma; Myxoma; Hemangioma; Lipoma; Lipoblastoma; Myelolipoma**
- ***Borderline*– Mucinous Cystadenoma-Borderline Mucinous Tumor; Primary Pulmonary Thymoma; Primary Pulmonary Meningioma; Intrapulmonary Teratoma; Well-differentiated Papillary Mesothelioma; Intrapulmonary Paraganglioma; Multicystic Mesothelial Proliferation**