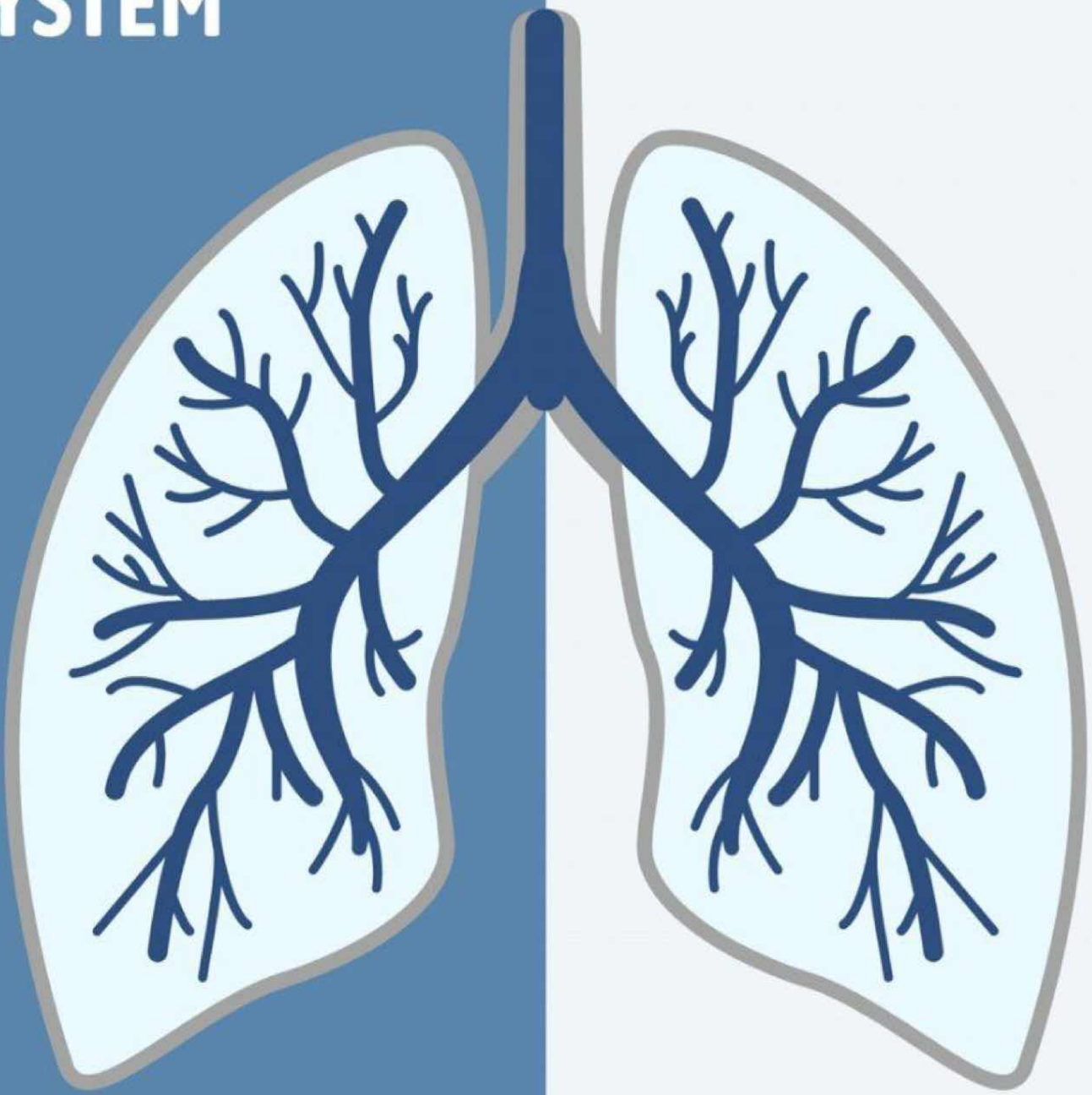


# RESPIRATORY SYSTEM

# PATHOLOGY



WRITER:

018 sheets



CORRECTOR:

Sawsan alqeam



DOCTOR:

Maram abdaljaleel



We will continue talking about **lung carcinomas**:

1. Adenocarcinoma (lecture 7)
2. Squamous cell carcinoma (lecture 7)

### **3. Small cell carcinoma (SCLC)**

### **4. Large cell carcinoma**

## **SCLC- Small Cell Lung Carcinoma**

They are centrally located with extension into the lung parenchyma.

By the time of diagnosis, most will have metastasis to **hilar and mediastinal nodes**.

In the 2015 WHO Classification, SCLC is grouped together with **large cell neuroendocrine carcinoma** (another very aggressive tumor that exhibit neuroendocrine morphology and expresses neuroendocrine markers).

## **MORPHOLOGY**

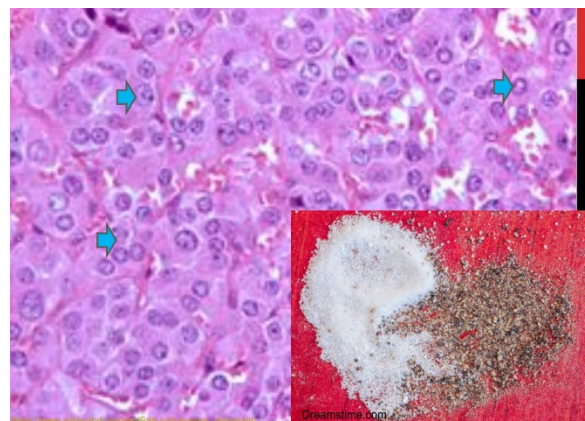
SCLS generally appear as pale grey tumor.

Histologically, they are composed of a relatively small tumor cells, with a round to fusiform shape, scant cytoplasm, finely granular chromatin - **salt and pepper appearance**.

Cells are twice the size of resting lymphocytes.

**This figure shows the histology of SCLC:**

As you can see there is monomorphic proliferation of relatively small cells, with finely granular chromatin.



The appearance of finely stabbed nuclei resembles **salt & pepper** mix.

SCLC shows **frequent mitotic figures**.

Almost always associated with **Necrosis**, which can be extensive.

Fragile tumor cells with “crush artifact”, especially in small biopsy specimens.

**Nuclear molding** due to **close position of tumor cells** that have scant cytoplasm.

Express **neuroendocrine markers**. (used to highlight the neuroendocrine differentiation in pathology lab)

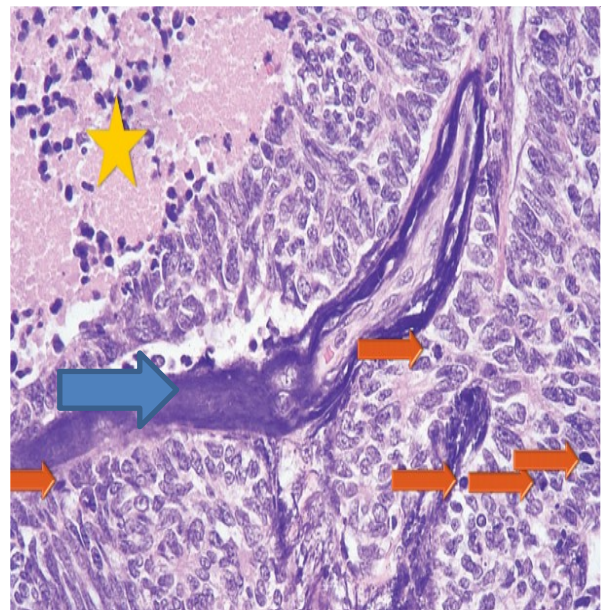
They also secrete polypeptide hormones that may result in **paraneoplastic syndromes**. (A syndrome that happens as a consequence to hormones and cytokines, released as a part of the immune response to the presence of the tumor, or from the tumor cells themselves)

This figure shows proliferation of small round/oval blue cells with salt and pepper nuclei and frequent mitotic figures.

**Red arrows** point to mitotic figures

**Yellow star** points to an area of extensive necrosis.

**The blue arrow** shows basophilic staining of vascular walls, due to encrustation by and from necrotic tumor cells (**this is called the Azzopardi effect**).



## **Large cell carcinoma**

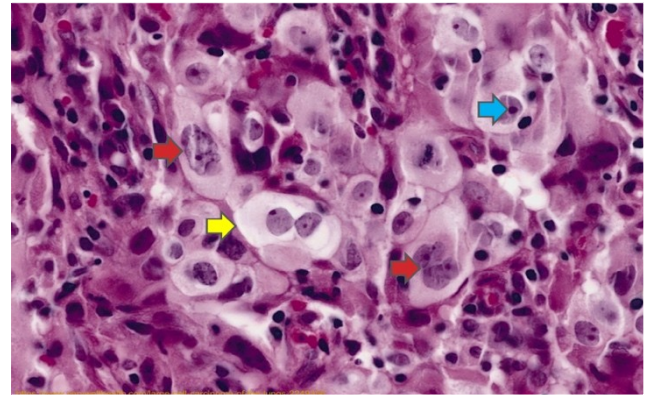
They are undifferentiated, malignant epithelial tumors. (which means that the cells in this tumor don't look like the differentiated tissue, so they show no evidence of glandular or squamous differentiation like “adenocarcinoma or squamous cell carcinoma”).



Lack cytologic features of small cell carcinoma and have no glandular or squamous differentiation.

Histologically, they have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm.

This figure shows the histologic features in large cell carcinoma, the cells are **large in size**, the **nuclei are large and polymorphic** in size and shape with the presence of prominent nuclei. There is **no squamous or glandular differentiation**.



Mixed patterns are seen in about 10% of cases (e.g., adenosquamous carcinoma, mixed adenocarcinoma, small cell carcinoma).

## **SPREAD AND METASTASIS of lung tumors**

Each of the Tumor types tends to spread to lymph nodes around the carina, mediastinum, and in the neck and clavicular regions, and distant sites.

Left supraclavicular lymph node (aka. **Virchow node**) involvement is particularly characteristic. Sometimes, it is the first clue for the presence of an occult primary tumor. (which means the first presentation in a patient who already has lung carcinoma is **the supra clavicular lymph node enlargement**).

These tumors, when advanced, extend into the pleural or pericardial space, leading to inflammation and effusion. They may compress or infiltrate to the SVC, either **venous congestion or the vena caval syndrome**.

**Pancoast tumors (Pancoast syndrome)**: Apical lung carcinoma, invading the brachial or cervical sympathetic plexus, to cause:

- A. Severe pain in the distribution of the ulnar nerve.



- B. Horner syndrome (ipsilateral enophthalmos, ptosis, miosis, and anhidrosis).
- C. Destruction of the first and second ribs and sometimes thoracic vertebrae.

**Tumor-Node-Metastasis (TNM)** categories are used to indicate **the size and spread** of the primary neoplasm. (so, they point to the anatomic extent of the lung cancer and predict the overall survival of patients with SCLC & Non-SCLC. **The T stands for the tumor size**, which has important prognostic relevance, as each centimeter increase in size from less than 1cm, up to 5cm yields a significantly different prognosis.

**The N stands for regional lymph node involvement**, where it includes the anatomic nodal involvement & the number of involved lymph nodes, which means that there is quantitate and qualitative assessment of LN involvement.

**The M stands for distant metastasis**, which also includes malignant pleural effusions or malignant pericardial effusions.

## **CLINICAL COURSE**

- Mostly Silent, insidious lesions
- Chronic cough and expectoration (Usually the first presentation)
- Hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion (by the time these symptoms are noted, the prognosis is already poor because they result from the direct extension of the tumor into adjacent such as the recurrent laryngeal nerve causing hoarseness of voice, the superior vena cava causing SVC syndrome, and pleural or pericardial spaces causing malignant pericardial or pleural effusion).
- Persistent segmental atelectasis or pneumonitis. (caused by an obstruction of the tumor to a part of the airways), also indicates poor prognosis.
- Symptoms from metastatic spread:
  - A. Brain (mental or neurologic changes)
  - B. Liver (hepatomegaly),

C. Bones (pain).

Although the adrenal glands may be obliterated by metastatic disease, adrenal insufficiency (Adison disease) is uncommon. (still functions even if there is infiltration to the gland)

## **PROGNOSIS, NSCLC: (Non-SCLS)**

- NSCLCs (Adenocarcinoma and Squamous cell carcinoma) carry a better prognosis than SCLCs.
- If NSCLCs detected before metastasis or local spread, cure is possible by **lobectomy or pneumonectomy**.
- SCLCs, invariably spread by the time they are first detected even if the primary tumor appears to be small and localized, so surgical resection is not a viable treatment.
- SCLC are very sensitive to chemotherapy but invariably associated with recurrence.
- Median survival even with treatment is 1 year only, 5% are alive in 10 years.

## **PARANEOPLASTIC SYNDROMES**

They are group of clinical disorders associated with malignant diseases (**most commonly lung cancers, because the histology of lung cancers influences the type of associated paraneoplastic syndrome**) and are not directly related to the physical effect of the primary or metastatic tumors.

About 10% of lung cancer patients develop paraneoplastic syndrome.

These conditions arise from the secretions of the functional peptides or the hormones from the tumor cells themselves, or from inappropriate immune reaction between normal host cell and the tumor cells.

We have 7 types of paraneoplastic syndromes, which are:

(1) Hypercalcemia (secretion of a PTH related peptide) **MOST COMMON**

Usually associated with **squamous cell carcinoma**.

(2) Cushing syndrome (production of ACTH) mostly associated with **neuroendocrine lung tumors**, can be seen in carcinoid tumors and SCLC.

(3) Syndrome of inappropriate secretion of ADH (common) mostly associated with **SCLC**.

(4) Acromegaly (growth hormone-releasing hormone (GHRH) or growth hormone (GH)) mostly associated with **bronchial carcinoids and SCLC**.

(5) Neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis

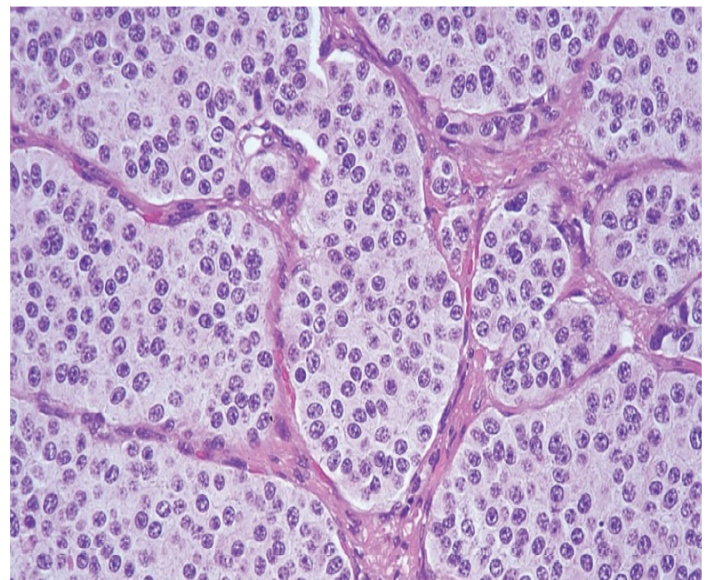
(6) Clubbing of the fingers and hypertrophic pulmonary osteoarthropathy (**Adenocarcinomas and squamous cell carcinomas**)

(7) Coagulation abnormalities, including migratory thrombophlebitis, nonbacterial endocarditis, and DIC.

## **CARCINOID TUMORS**

Malignant tumors involving the lungs.

- 5% of all pulmonary neoplasms.
- Malignant tumors, low-grade neuroendocrine carcinomas.
- Composed of cells containing dense-core neurosecretory granules in their cytoplasm and, rarely, may secrete hormonally active polypeptides.
- Sub-classified as **typical** or **atypical**; both are often resectable and curable.





- May occur as part of the multiple endocrine neoplasia syndrome (MEN syndrome)
- Young adults (mean 40 years)
- 5% to 15% of carcinoids have metastasized to the **hilar nodes** at presentation
- Distant metastases are **rare**

## **MORPHOLOGY, MACROSCOPICALLY:**

Originate in main bronchi mostly, Peripheral carcinoids are less common

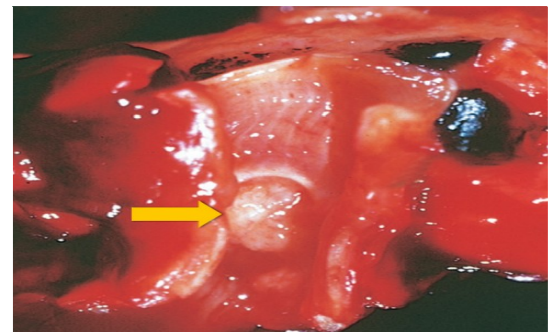
- Well demarcated
- Grow in one of two patterns:
  1. An obstructing polypoid, spherical, intraluminal mass.
  2. a mucosal plaque penetrating the bronchial wall to fan out in the peribronchial tissue—called **collar-button lesion**.



The figure at the top shows an obstructive polypoid tumor (Yellow arrow) within the lumen of the bronchus (1<sup>st</sup> growth pattern)

The figure below, shows a collar button appearance, it has 2 surfaces, one is wider than the other. (2<sup>nd</sup> growth pattern)

This figure shows a carcinoid tumor growing as a spherical mass into the lumen of the bronchus.



## MORPHOLOGY, MICROSCOPICALLY:

- **Typical carcinoids:** composed of nests of uniform cells that have regular round nuclei with “salt-and-pepper” chromatin, absent or rare mitoses and little pleomorphism
- **Atypical carcinoid:** tumors display a higher mitotic rate and small foci of necrosis. These tumors have a higher incidence of lymph node and distant metastasis than typical carcinoids. (about 20% to 40% of atypical carcinoid patients have TP53 mutations)

This figure shows histologic findings in typical carcinoids, the tumor is composed of **multiple nests** (عش العصفور-) each contains uniform cells that have regular round nucleus, with salt and pepper chromatin, with no increased mitotic activity (no necrosis can be identified in this figure)



## CLINICALLY:

Mostly manifest with signs and symptoms related to their intraluminal growth, including cough, hemoptysis, and recurrent bronchial and pulmonary infections.

As a result, peripheral tumors are often asymptomatic and discovered incidentally.

Rarely induces the **carcinoid syndrome**: intermittent attacks of diarrhea, flushing, and cyanosis.

## PROGNOSIS:

5- and 10-year survival rates:

For typical carcinoids are above 85%

For atypical carcinoid 56% and 35%, respectively

# **Malignant Mesothelioma**

- Rare cancer of mesothelial cells lining parietal or visceral pleura.
- Less commonly in the peritoneum and pericardium.
- Highly related to exposure to airborne asbestos (80% to 90% of cases):
- Not limited to people working with asbestos, but also anyone living in close proximity to an asbestos factory or being a relative of an asbestos worker.
- Long latent period: **25 to 40 years** after initial asbestos exposure. (long)
- The combination of cigarette smoking, and asbestos exposure DOES NOT increase the risk of developing malignant mesothelioma BUT INCREASES the risk for developing lung carcinoma.
- Once inhaled, asbestos fibers remain in the body for life.
- The lifetime risk after exposure DOES NOT diminish over time (unlike smoking, in which the risk decreases after cessation).

## **MORPHOLOGY, MACROSCOPIC:**

- Preceded by extensive pleural fibrosis and plaque formation (seen in CT scans)
- The tumor begins in a localized area and over time spread widely, either by contiguous growth or by diffusely seeding the pleural surfaces.
- May directly invade the thoracic wall or sub pleural lung tissue, but distant metastases are rare.

Upon autopsy, the affected lung is typically ensheathed by a layer of yellow-white, firm, variably gelatinous tumor that obliterates the pleural space. In this figure, the tumor appears as a thick firm white pleural tumor that ensheathes this lung.



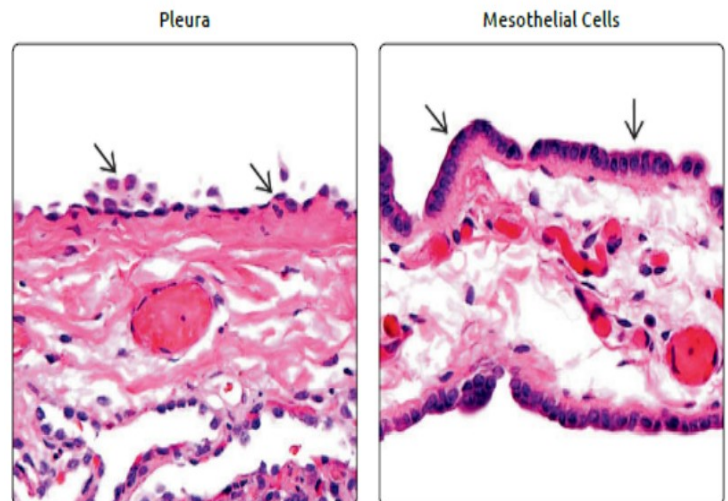


## NORMAL HISTOLOGY:

Normal mesothelial cells are biphasic, giving rise to pleural lining cells as well as the underlying fibrous tissue.

The right figure shows the normal histology of benign normal mesothelial cells, with lining epithelial cells and underlying fibrous tissue.

The left figure shows the pleura, lined by a single layer of normal mesothelial cells, these mesothelial cells are almost flat (small cuboidal) with eosinophilic cytoplasm and indistinct nuclear features.



## MORPHOLOGY, MICROSCOPIC:

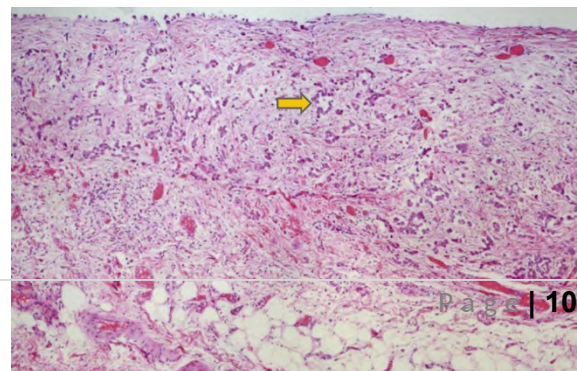
Microscopically, mesothelioma have one of three morphologic appearances:

(1) Epithelial: cuboidal cells with small papillary buds line tubular and microcystic spaces (**the most common** & confused with pulmonary adenocarcinoma).

(2) Sarcomatous: spindled cells grow in sheets.

(3) Biphasic: both sarcomatous and epithelial areas.

This figure shows the histology of mesothelioma, the arrow points to **plump rounded cells forming a gland-like configuration.**



## Cases

A 48-year-old gentleman developed truncal obesity, back pain, and skin that bruises easily over the past 8 months. On physical examination, he is afebrile, and his blood pressure is 160/95 mm Hg. A CXR shows an ill-defined, 5cm mass involving the left hilum of the lung. Cytologic examination of bronchial washings from bronchoscopy shows round epithelial cells that have the appearance of lymphocytes but are larger. The patient is told that, although his disease is apparently localized to one side of the chest cavity, surgical treatment is unlikely to be curative. He also is advised to stop smoking. Which of the following neoplasms is most likely to be present in this patient?

\*Truncal obesity, back pain, and skin that bruises easily indicates to Cushing syndrome (Increased ACTH secretion) \*

- A) Adenocarcinoma
- B) Bronchial carcinoid
- C) Adenocarcinoma in situ (Bronchioloalveolar carcinoma)

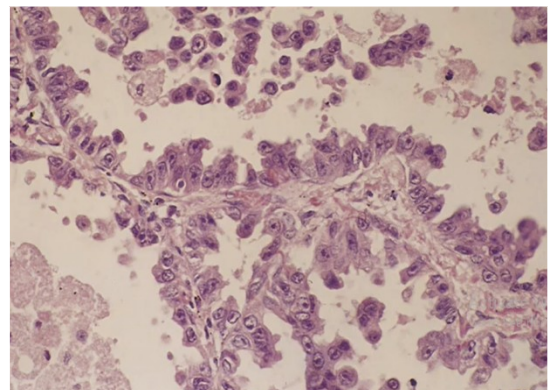
### D) Small cell carcinoma

A 55-year-old lady presented with cough and pleuritic chest pain for 3 weeks. Patient is afebrile. Some crackles are audible over the left lower lung on auscultation. A CXR shows ill-defined area of opacification in the left lower lobe. After 1 month of antibiotic therapy, her condition has not improved. CT-guided needle biopsy is performed, and the specimen is shown in the figure. Which of the following neoplasms is most likely to be present in this patient?

- A) Large cell anaplastic carcinoma

### B) Adenocarcinoma in situ

- C) Malignant mesothelioma
- D) Squamous cell carcinoma



# AMBOSS

Lung neuroendocrine tumors			
Small cell lung cancer (SCLC)	<ul style="list-style-type: none"> <li>Central</li> </ul>	<ul style="list-style-type: none"> <li>Strong association with <b>smoking</b> (extremely rare in nonsmokers)</li> <li>Associated with several <b>paraneoplastic syndromes</b> (see "Paraneoplastic syndromes" in "Clinical features" below)</li> <li>Undifferentiated and very aggressive with early metastases</li> <li>Associated mutations: L-myc oncogene</li> </ul>	<ul style="list-style-type: none"> <li>Neuroendocrine <b>Kulchitsky cells</b></li> <li>Rapid growth pattern</li> <li>Expressed tumor markers                             <ul style="list-style-type: none"> <li>Chromogranin A</li> <li>Synaptophysin</li> <li>Neuron-specific enolase</li> </ul> </li> </ul>
Large cell neuroendocrine carcinoma	<ul style="list-style-type: none"> <li>Peripheral</li> </ul>	<ul style="list-style-type: none"> <li>Generally, high-grade tumors</li> <li>Poor clinical prognosis</li> </ul>	
Bronchial carcinoid tumor	<ul style="list-style-type: none"> <li>Central/peripheral</li> </ul>	<ul style="list-style-type: none"> <li>Accounts for 1–2% of all lung cancers but are the most common primary lung cancer in children and adolescents</li> <li>Good prognosis with an indolent course</li> <li>Metastases are rare.</li> <li>Carcinoid syndrome (e.g., flushing, diarrhea) is rare</li> <li>Mass effect of tumor (e.g., wheezing)</li> </ul>	

## Mesothelioma

- Definition:** malignant tumor that develops from mesothelial cells
- Epidemiology**
  - Sex: ♂ > ♀ (3:1)
  - Age range: ~ 40–70 years
- Etiology**
  - Secondary to **asbestos** exposure
  - Alcohol, smoking, and diet do not increase the incidence of mesothelioma.
- Localization**
  - Pleural mesothelioma** (most common)
  - Peritoneal mesothelioma** (rarely)
  - Pericardial mesothelioma** (very rarely)
- Clinical findings**
  - Dyspnea and nonpleuritic chest pain (most common)
  - Fever, sweats, weight loss, fatigue
  - Features of pleural effusion: dull percussion; absent or reduced breath sounds on affected side
- Diagnosis**
  - Pleurocentesis: **bloody** (exudative) pleural effusion
  - Imaging (chest x-ray and CT)
    - Multiple nodular pleural lesions (**pleural thickening**)
    - Ipsilateral hemothorax**
    - Reduced size of **ipsilateral lung fields**
    - Obliteration of the diaphragm
  - Laparoscopy, thoracoscopy, and pleuroscopy with stained biopsy: reveals mesothelioma cells and **psammoma bodies**
    - The procedures carry risk of **implantation metastasis**.
    - It is important to differentiate mesothelioma from adenocarcinoma.
      - Immunohistochemistry: mesothelioma often stains positive for mesothelin, serum mesothelin-related protein (SMRP), **calretinin**, cytokeratin 5/6, and vimentin.
      - Microvilli in mesothelioma are long and slender; they are short and stubby in adenocarcinoma.



Endocrine	Cushing syndrome	<ul style="list-style-type: none"> <li>Neoplastic tissue produces <b>ectopic ACTH</b> (occasionally with CRH) → increased cortisol in the adrenal glands</li> </ul>	<ul style="list-style-type: none"> <li>SCLC</li> <li>Pancreas cancer</li> <li>CNS tumors</li> </ul>	<ul style="list-style-type: none"> <li>Moon facies, buffalo hump</li> <li>Hirsutism, hyperpigmentation</li> <li>Lethargy, depression, sleep disturbance</li> <li>Osteopenia, osteoporosis</li> <li>Muscle atrophy/weakness</li> </ul>
	Syndrome of inappropriate ADH secretion	<ul style="list-style-type: none"> <li>Neoplastic tissue produces <b>ectopic ADH (endogenous)</b> → increased free-water reabsorption and retention and hyponatremia</li> </ul>	<ul style="list-style-type: none"> <li>SCLC</li> <li>CNS tumors</li> </ul>	<ul style="list-style-type: none"> <li>Anorexia, nausea, vomiting</li> <li>Headache</li> <li>Muscle cramps, muscle weakness</li> <li>Lethargy, confusion</li> </ul>
	Hypercalcemia of malignancy	<ul style="list-style-type: none"> <li><b>Humoral hypercalcemia of malignancy (pseudohyperparathyroidism):</b> PTHrP secretion by the tumor</li> </ul>	<ul style="list-style-type: none"> <li>Squamous cell carcinomas (lung, head, and neck)</li> <li>Renal cancer</li> <li>Bladder cancer</li> <li>Breast cancer</li> <li>Ovarian cancer</li> </ul>	<ul style="list-style-type: none"> <li>Nephrolithiasis, nephrocalcinosis</li> <li>Bone pain, arthralgias, myalgias</li> <li>Constipation, abdominal pain</li> <li>Nausea, vomiting, anorexia</li> </ul>
		<ul style="list-style-type: none"> <li>Ectopic vitamin D production due to <b>1<math>\alpha</math>-hydroxylase</b> activity in tumor cells</li> <li><b>Local osteolytic hypercalcemia:</b> osteolytic activity at sites of skeletal metastases</li> </ul>	<ul style="list-style-type: none"> <li>Hodgkin lymphoma</li> <li>NHL</li> <li>Multiple myeloma</li> <li>Breast cancer</li> </ul>	
Skeletal	Hypertrophic pulmonary osteoarthropathy (Bamberg-Marie syndrome)	<ul style="list-style-type: none"> <li>Likely ectopic vascular endothelial GF, platelet-derived GF, and/or prostaglandin E2 → increased angiogenesis as well as fibroblast and osteoblast activity → connective-tissue matrix and bone synthesis</li> </ul>	<ul style="list-style-type: none"> <li>NSCLC (especially lung adenocarcinoma)</li> </ul>	<ul style="list-style-type: none"> <li>Features include digital clubbing, joint pain, thickening of tubular bones, periostosis, and joint effusions</li> </ul>