PATHOLOGY

RESPIRATORY SYSTEM

SHEET NO. **8**

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بسم الله الرحمن الرحيم

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 (usually the only one) 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**.
Vena caval syndrome patients present with swelling in the head & neck area, shortness of breath, and sometimes difficulty in swallowing.

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(posterior displacement of the eye), ptosis(dropping of upper eyelid), miosis(reduction in pupil size), and Anhidrosis(loss of sweating)).

C. Destruction of the first and second ribs and sometimes thoracic vertebrae.
As you notice, many of the presentations are not related to respiratory system manifestations.

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:

• Lung cancer is one of the most insidious and aggressive Neoplasms (Mostly Silent).

• The major presenting complaints are cough (75%), weight loss (40%), chest pain (40%), and dyspnea (20%).

- Most patients are asymptomatic, but if they do have symptoms this is what they come with.

• 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)
- a patient with no symptoms suddenly presents with change in mental status or gets an attack of seizure, through brain CT scan found to have a tumor or multiple, then full CT scan is taken to eventually discover primary lung cancer that metastasized.

B. Liver (hepatomegaly),

- a patient comes with multiple liver nodules and abnormal liver function test, then through biopsy and CT scan was found to have lung cancer.

C. Bones (pain).

- a patient presents with severe back pain that doesn't go away with analgesics or any other type of medication, radiology → lung cancer.

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:

• **Prognosis is poor** for most patients.
• Even with thoracic surgery, radiation therapy, and chemotherapy:

- the overall 5-year survival rate is only 18.7%.
- The 5-year survival rate is:
  - 52% for cases detected when the disease is still localized,so can be removed surgically like adenocarcinoma and squamous cell carcinoma.
  - 22% when there is regional metastasis
  - only 4% with distant metastases(pleura, pericardiam,liver,brain,bone)

• 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.

• most patients present with advanced stage disease;
• despite excellent initial responses to chemotherapy, the median survival is approximately **10 months** and the cure rate is close to **zero.** (because of its rapid spreading)

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, parathormone, prostaglandin E2) **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.**
- increase in ADH causes retention which eventually leads to **hyponatremia.**

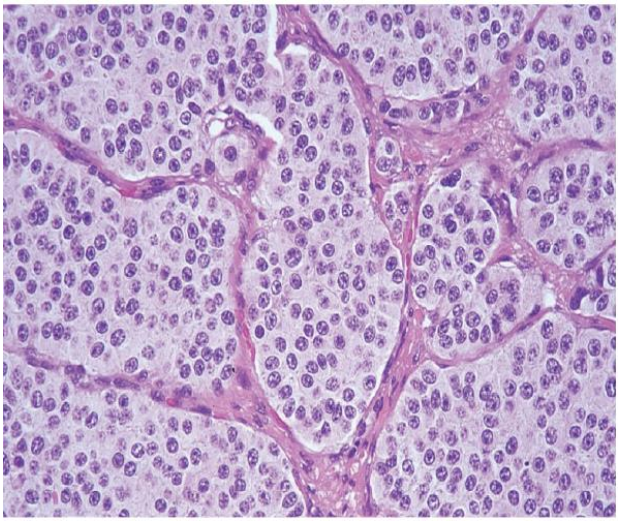
(4) Acromegaly (growth hormone-releasing hormone (GHRH) or growth hormone (GH)) mostly associated with **bronchial carcinoids and SCLS.**

(5) Neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis. (Dr only read neuromuscular syndromes)

(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.

•2- 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 (only 10% of cases)

• Sub-classified as **typical** or **atypical**; both are often resectable and curable

• May occur as part of the multiple endocrine neoplasia syndrome (MEN syndrome)

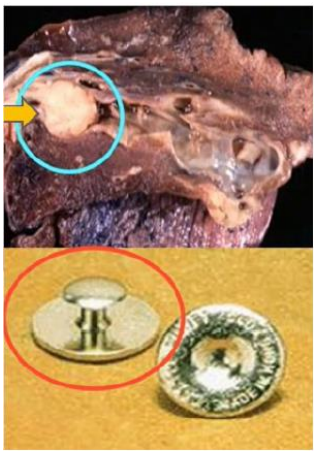
• Young adults (mean 40 years)

• 5% to15% of carcinoids have metastasized to the **hilar nodes** at Presentation

• Distant metastases are **rare.**

MORPHOLOGY, MACROSCOPICALLY:

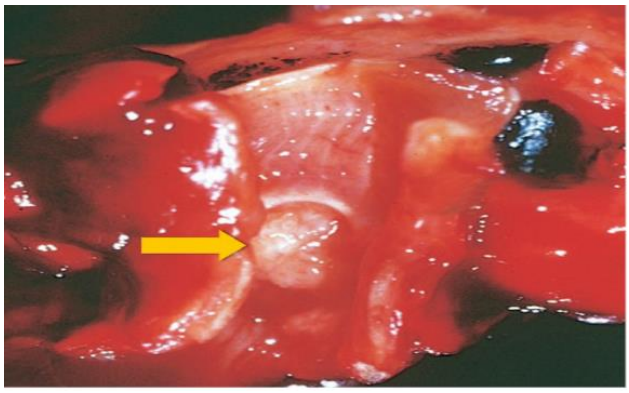
Originate in main bronchi mostly, Peripheral carcinoids are less common
• Well demarcated
• Grow in one of two patterns:
1. An obstructing polypoid, spherical, intraluminal mass.(most common)
2. a mucosal plaque penetrating the bronchial wall to fan out in the peribronchial tissue—-called **collar-button lesion**



The figure at the top shows an obstructive polypoid tumor (Yellow arrow) within the lumen of the bronchus (1st growth pattern).
-exophytic mass

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

-endophytic mass



This figure shows a carcinoid intrabronchial polypoid tumor growing as a spherical mass into the lumen of the bronchus. If it was larger, it would cause obstruction of bronchial wall.

MORPHOLOGY, MICROSCOPICALLY:

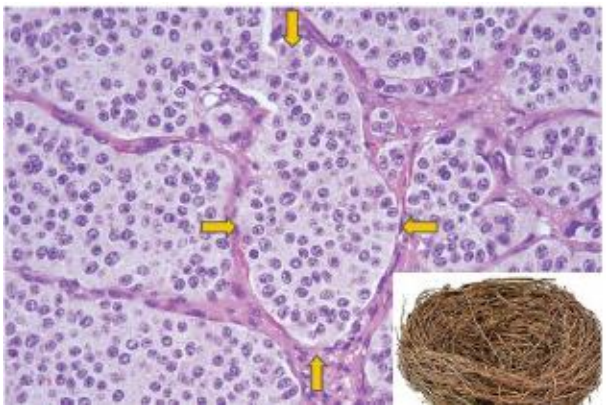
• **Typical carcinoids**: composed of nests of uniform cells that have regular round nuclei with "salt-and-pepper" chromatin, abundant cytoplasm, absent or rare mitoses, no necrosis and little pleomorphism.
Not aggressive, maximum mitosis is <2 per 10 HPF mitotic figures.

• **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).
-higher degree of mitosis: 2-10/10 of HPF mitotic figures.

Main difference between them is rate of mitosis.

Extra: mitotic activity is given as a mitotic count, expressed as the number of mitoses per high-power field (HPF), or per 10 or 50 HPFs.

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). No atypia, and if found it's usually very minimal.



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. It's due to release of active peptides like serotonin.

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.

- Most common manifestation: mesothelial plaques
- Worst manifestation: development of any type of cancer (laryngeal/lung/mesothelioma)

• 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).

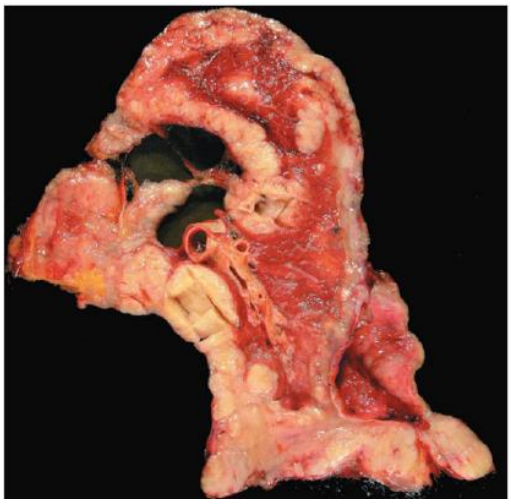
MORPHOLOGY, MACROSCOPIC:

• 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.

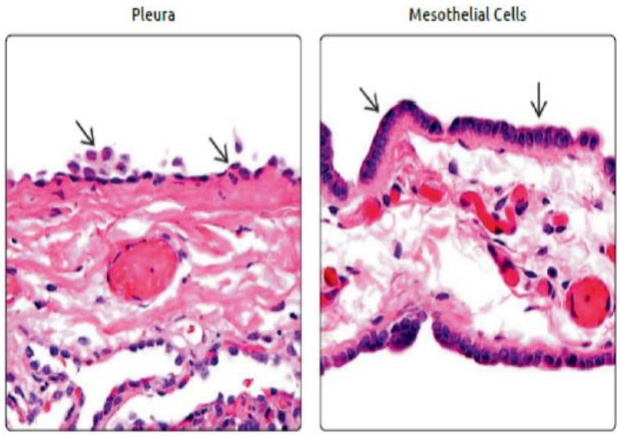
Upon autopsy, the affected lung is typically ensheathed by a layer of yellow-white, firm, variably gelatinous tumor that obliterates the pleural space. In this figure, the tumor appears as a thick firm white pleural tumor that ensheathes this lung.



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:

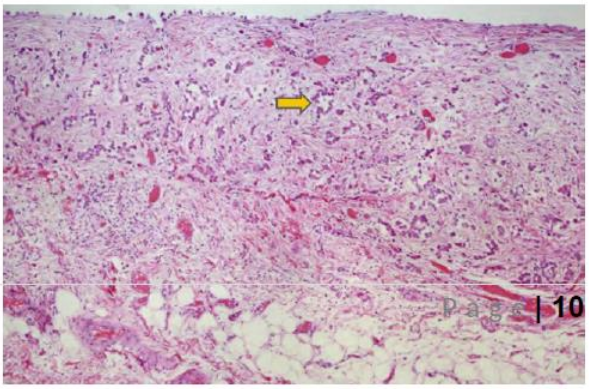
Microscopically, mesothelioma have one of three morphologic appearances:

(1)Epithelial: cuboidal cells with small papillary buds line tubular and microcystic spaces (**the most common** & confused with pulmonary adenocarcinoma).
- in a histology section of pleural nodule with epithelial proliferation; the cause could be one of the following: lung cancer that metastasized to pleura, or mesothelioma of the pleura itself, or distant metastasis from other organs like GI. Immunostains are used to confirm the origin of the tumor. If a patient is a female then you have to rule out breast and gastric cancer, for males you rule out prostate and gastric cancer

(2) Sarcomatous: spindled cells grow in sheets.

(3) Biphasic: both sarcomatous and epithelial areas.

This figure shows the histology of mesothelioma, infiltration by epithelial cells. The arrow points to **plump rounded cells forming a glandlike configuration.**



CLINICAL FEATURES:

• The presenting symptoms are chest pain, dyspnea, and recurrent pleural effusions.

• In 20% Concurrent pulmonary asbestosis

• The lung is invaded directly

• often metastatic spread to the hilar lymph nodes

• liver and other distant organs metastasis (not very common)

• 50% die within 12 months of diagnosis

الخلاصة: لا تدخنوا :(

CASES:

1. A 69-year-old gentleman**, smoker**, presented with cough and a 7 kg weight loss over the past 4 months. Physical examination shows **finger clubbing**. He is afebrile. CXR shows **no hilar adenopathy**, but there is **cavitation** within a 3-cm lesion near the right hilum. Labs show **elevated serum calcium**. Bronchoscopy shows a lesion occluding the **right main bronchus** (centrally located) **A surgical procedure with curative intent is attempted.** Which of the following neoplasms is most likely to be present in this patient?

   A. adenocarcinoma in situ
   B. squamous cell carcinoma
   C. metastatic renal cell carcinoma
   D. small cell anaplastic carcinoma

B

2. A 57-year-old **lady** presented with chronic nonproductive cough for 4 months along with loss of appetite and a 7 kg weight loss. **She does not smoke**. On physical examination, no remarkable findings. Her CXR shows a right **peripheral subpleural mass**. A fine-needle aspiration biopsy is performed, and she undergoes a right lower lobectomy. Microscopically the proliferating cells show **glandular differentiation**. Which of the following neoplasms did she most likely have?

   A. Adenocarcinoma
   B. Bronchial carcinoid
   C. Hamartoma
   D. Squamous celll carcinoma

A

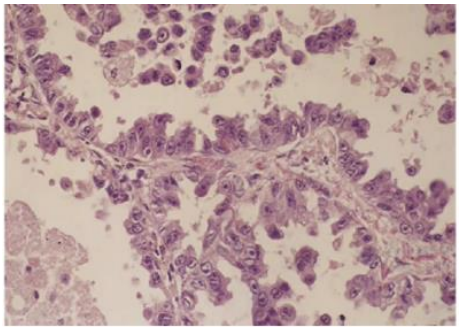
Even if mesothelioma is one of the choices you wouldn't choose it as the lesion is subpleural, usually mesothelioma involves the pleura +usually older age bcz of 40 year exposure

3. A 48-year-old gentleman developed **truncal obesity, back pain, and skin that bruises easily over the past 8 months** (cushing syndrome). 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?

   A. Adenocarcinoma
   B. Bronchial carcinoid
   C. Adenocarcinoma in situ (Bronchioalveolar carcinoma)
   D. Small cell carcinoma

D

4. 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 aplastic carcinoma
   B. Adenocarcinoma in situ
   C. Malignant mesothelioma
   D. Squamous cell carcinoma



Explanation:

The lady was treated as if she had pneumonia, so this tumor radiolagically showed consolidation and its usually peripherally located. Antibiotics were not effective, so a biopsy was taken as shown. It shows air spaces lined by cells that rest on basement memebrant **with no stromal invasion**. "Ill-defined area of opacification in the left lower lobe", means the area was easily recognized so it's larger than 5 mm.

So→ **B**

Here's a table from pathoma summarizing all lung tumors and their features:

CANCER	CHARACTERISTIC HISTOLOGY	ASSOCIATION	LOCATION	COMMENT
Small cell carcinoma	Poorly differentiated small cells (Fig. 9.19); arises from neuroendocrine (Kulchitsky) cells	Male smokers	Central	Rapid growth and early metastasis; may produce ADH or ACTH or cause Eaton-Lambert syndrome (paraneoplastic syndromes)
Squamous cell carcinoma	Keratin pearls or intracellular bridges (Fig. 9.20A,B)	Most common tumor in male smokers	Central (Fig. 9.20C)	May produce PTHrP
Adenocarcinoma	Glands or mucin (Fig. 9.21A)	Most common tumor in nonsmokers and female smokers	Peripheral (Fig. 9.21B)	
Large cell Carcinoma	Poorly differentiated large cells (no keratin pearls, intercellular bridges, glands, or mucin)	Smoking	Central or peripheral	Poor prognosis
Bronchioloalveolar carcinoma	Columnar cells that grow along preexisting bronchioles and alveoli (Fig. 9.22); arises from Clara cells	Not related to smoking	Peripheral	May present with pneumonia-like consolidation on imaging; excellent prognosis
Carcinoid tumor	Well differentiated neuroendocrine cells; chromogranin positive (Fig. 9.23A,B)	Not related to smoking	Central or peripheral; classically forms a polyp-like mass in the bronchus (Fig. 9.23C)	Low-grade malignancy; rarely, can cause carcinoid syndrome
Metastasis to lung	Most common sources are breast and colon carcinoma.		Multiple 'cannon-ball' nodules on imaging	More common than primary tumors

Lung neuroendocrine tumors			

Small cell lung cancer (SCLC)	• Central	• Strong association with **smoking** (extremely rare in nonsmokers)
		• Associated with several **paraneoplastic syndromes** (see "Paraneoplastic syndromes" in "Clinical features" below)
		• Undifferentiated and very aggressive with early metastases [16]
		• Associated mutations: L-myc oncogene [17]
			• Neuroendocrine **Kulchitsky cells** [18]
			• Rapid growth pattern
			• Expressed tumor markers
			  ◦ Chromogranin A
			  ◦ Synaptophysin
			  ◦ Neuron-specific enolase

Large cell neuroendocrine carcinoma	• Peripheral	• Generally, high-grade tumors • Poor clinical prognosis	
Bronchial carcinoid tumor	• Central/peripheral	• Accounts for 1–2% of all lung cancers but are the most common primary lung cancer in children and adolescents • Good prognosis with an indolent course [19] • Metastases are rare. • Carcinoid syndrome (e.g., flushing, diarrhea) is rare • Mass effect of tumor (e.g., wheezing)	

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. [6]
    - 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. [7]
      - Microvilli in mesothelioma are long and slender; they are short and stubby in adenocarcinoma.

Endocrine	**Cushing syndrome**	• Neoplastic tissue produces **ectopic ACTH** (occasionally with CRH) → increased cortisol in the adrenal glands	• SCLC • Pancreas cancer • CNS tumors	• Moon facies, buffalo hump • Hirsutism, hyperpigmentation • Lethargy, depression, sleep disturbance • Osteopenia, osteoporosis • Muscle atrophy/weakness
	Syndrome of inappropriate ADH secretion	• **Neoplastic tissue produces ectopic ADH (endogenous)** → increased free-water reabsorption and retention and hyponatremia	• SCLC • CNS tumors	• Anorexia, nausea, vomiting • Headache • Muscle cramps, muscle weakness • Lethargy, confusion
	Hypercalcemia of malignancy	• **Humoral hypercalcemia of malignancy** (pseudohyperparathyroidism): **PTHrP** secretion by the tumor	• Squamous cell carcinomas (lung, head, and neck) • Renal cancer • Bladder cancer • Breast cancer • Ovarian cancer	• Nephrolithiasis, nephrocalcinosis • Bone pain, arthralgias, myalgias • Constipation, abdominal pain • Nausea, vomiting, anorexia
		• Ectopic vitamin D production due to **1α-hydroxylase** activity in tumor cells	• Hodgkin lymphoma • NHL	
		• **Local osteolytic hypercalcemia**: osteolytic activity at sites of skeletal metastases	• Multiple myeloma • Breast cancer	
Skeletal	**Hypertrophic pulmonary osteoarthropathy (Bamberger-Marie syndrome)**	• 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	• NSCLC (especially lung adenocarcinoma)	• Features include digital clubbing, joint pain, thickening of tubular bones, periostosis, and joint effusions