PATHOLOGY TEAM 439

MED439 KING SAUD UNIVERSITY

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جامعة الملك سعود King Saud University 1957

Tumors of The Lung

Objectives:

- Know the epidemiology of lung cancer
- Is aware of classification of bronchogenic carcinoma which include: squamous carcinoma, adenocarcinoma, small cell and large cell (anaplastic) carcinomas.
- Understand the predisposing factors of bronchogenic carcinoma.
- Understands the clinical features and gross pathology of bronchogenic carcinoma. Know the precursors of squamous carcinoma (squamous dysplasia) and adenocarcinoma (adenocarcinoma in situ and atypical adenomatous hyperplasia).
- Have a basic knowledge about neuroendocrine tumours with special emphasis on small cell carcinoma and bronchial carcinoid.
- Is aware that the lung is a frequent site for metastatic neoplasms.

Rikabi's content

Index:
Important
NOTES
Extra Information

Lung Tumors

- Most lung tumors are **malignant**.
- Benign tumors are well demarcated, unlike malignant tumors.
- Primary lung cancer is a common disease BUT metastatic tumors(1) are **more common** than the primary tumors.
- The most common benign lesions are **hamartomas**

Hamartoma : (Rikabi's content)

- An abnormal growth of tissue (or benign tumor), and the tissue causing the hamartoma is indigenous to the site from where it arised.
- Histo: Cartilage, blood vessels, glands, inflammatory cells, mesenchymal tissue, fat
- **Teratoma** could be benign or malignant, unlike hamartoma where it is always benign. (a tumor in which the constitution tissues arise from the 3 embryonic layers)
- Hamartoma is asymptomatic.
- Gross features of Hamartoma: Pale, well circumscribed, rounded solid lesion

Epidemiology of Lung Tumors

1. Primary lung cancer is the most common **fatal cancer** in both men and women worldwide.
   - **a.** Accounts for >30% of cancer deaths in men
   - **b.** Accounts for >25% of cancer deaths in women
2. Incidence of lung cancer is **declining in men** but **increasing in women**.
3. Peak incidence is at **55 to 65 years of age.**

Classification of bronchogenic carcinoma

TIP: UNDERSTANDING THE CLASSIFICATION AND THE TYPES OF LUNG CANCER IN THE BEGINNING WILL MAKE THE LECTURE WAY MORE EASIER TO STUDY AND UNDERSTAND

<table>
<tr><td rowspan="6">1</td><td rowspan="6">Malignant epithelial tumors
----OR-----
Bronchogenic carcinoma</td><td rowspan="3">Non-Small Cell Lung Carcinoma (NSCC)
Includes :</td><td>Squamous cell carcinoma</td></tr>
<tr><td>Adenocarcinoma</td></tr>
<tr><td>Large cell carcinoma</td></tr>
<tr><td colspan="2">Small cell lung carcinoma(SCC)</td></tr>
<tr><td colspan="2">Combine patterns</td></tr>
<tr><td colspan="2">Carcinoid tumor</td></tr>
<tr><td colspan="2">Others</td></tr>
</table>

(1) **Metastatic cancer :** is cancer that spreads from its site of origin to another part of the body.

cont.)
Classification of bronchogenic carcinoma

2	Malignant mesothelial tumor	Malignant mesothelioma	Epithelial
			Fibrous (spindle cell)
			Biphasic
3	Miscellaneous malignant tumor	Carcinosarcoma	
		Pulmonary blastoma	
		Melanoma	
		Lymphoma	
		Others	

(Rikabi's content)

Specific symptoms of lung tumors	General symptoms of tumors
parietal chest pain	anemia,fatigue،
unexplained coughing	non-intended weight loss
cachexia (because of TNF-α and IL-1)	unexplained fever
dyspnea	unexplained hypercalcemia
The patient could have COPD also	muscle wasting

*Clubbing of fingers may also be a symptom of tumors but can also be present with just COPD.

Classification of Malignant epithelial tumors of lung

I. Non-Small Cell Lung Carcinoma (NSCC) (70%-75%)

1) Squamous cell carcinoma (25%-35%)

2) Adenocarcinoma, including bronchioloalveolar carcinoma (30%-35%).

3) Large cell carcinoma (10%-15%).

II. Small cell lung carcinoma (SCLC) (20%-25%).

Both small cell carcinoma and carcinoids are neuroendocrine tumors as both arise from the neuroendocrine cells normally present in the lung

III. Combine patterns (5%-10%).

- Most frequent patterns:
- Mixed squamous cell ca and adenocarcinoma.
- Mixed squamous cell ca and SCLC.

IV. Carcinoid tumors

V. Others

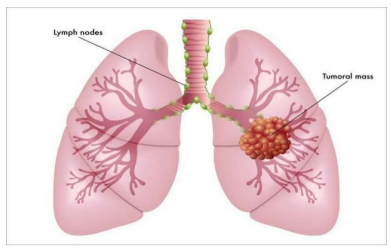
(Rikabi's content)

Mesothelioma

Bronchogenic carcinoma

Bronchogenic carcinoma is a malignant neoplasm of the lung arising from the epithelium of the lung.

- It is a common cause of cancer death in both men and women.



BRONCHOGENIC CARCINOMA

Non- Small cell lung carcinoma (NSCC)

which includes squamous cell, adenocarcinomas, and large-cell carcinomas.

1)**Surgical - offers the best chance for curing.**

2)Radiation - controls local disease, it is most commonly used to palliate symptoms.

3)Chemotherapy, not effective

4)Immunotherapy

For therapeutic purposes, bronchogenic carcinoma are classified into:

It is important to differentiated NSCC from SCC because the treatments are different.

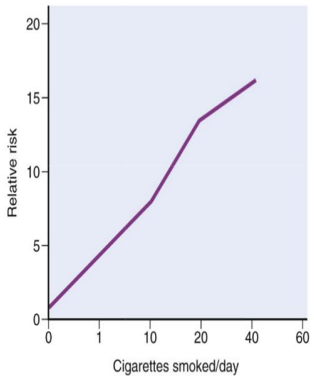
Small cell lung carcinoma (SCC)

Chemotherapy is very effective because small cell carcinomas are highly responsive to chemotherapy

Predisposing factors of bronchogenic carcinoma :

1. Tobacco smoking:

- Some 85% of lung cancers occur in cigarette smokers. Most types are linked to cigarette smoking, but the strongest association is with squamous cell carcinoma and small cell carcinoma.
- The nonsmoker who develops cancer of the lung usually has an adenocarcinoma.
- is directly proportional to the number of cigarettes smoked daily and the number of years of smoking.
- Cessation of cigarette smoking for at least 15 years brings the risk down.
- Passive smoking increases the risk to approximately twice than non-smokers.
- Cigarette smokers show various histologic changes, including squamous metaplasia of the respiratory epithelium which may progress to dysplasia, carcinoma in situ and ultimately invasive carcinoma.



- The risk of lung cancer is determined by the number of cigarettes smoked
- The risk is 20 to 40 times greater among habitual heavy smokers

Female smokers have a much greater risk of death from lung cancer and chronic obstructive lung disease in recent years than female smokers 20 or 40 years ago, reflecting changes in smoking behavior according to an article published in New England Journal of Medicine.

Female smokers today smoke more like men than women in previous generations, beginning earlier in adolescence and, until recently, smoking more cigarettes per day.

Other causes

2) Radiation:

All types of radiation may be carcinogenic and increase the risk of developing lung cancer. Tradium and uranium workers are at risk

3) Asbestos:

increased incidence of cancer with asbestos exposure, especially in combination with cigarette smoking.

Industrial exposure to **nickel and chromates, coal, mustard gas, arsenic, iron** etc.

4) Air pollution:

May play some role in increased incidence. Indoor air pollution especially by radon.

5) Scarring:

sometimes old infarcts, wounds, scar, granulomatous infections are associated with adenocarcinoma.

Precursor lesions

- Squamous dysplasia and carcinoma in situ can lead to: **Squamous cell carcinoma**
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia can lead to: **Neuroendocrine tumors**
- Atypical adenomatous hyperplasia can lead to: **Adenocarcinoma**

- It should be noted that the term "precursor" does not imply that progression to invasion will occur in all cases.
- Ex;(a man was smoking for 4 years as result he develop precursor lesions but not necessary he's gunna develop a cancer

Bronchogenic carcinoma site

Central tumors
- Squamous cell CA
- Small cell CA

Peripheral tumors
- **Adenocarcinoma**
  - bronchial derived
  -bronchioloalveolar ca
- Large cell carcinoma

A. Squamous cell carcinoma (SqCC)

Epidemiology

- Second most common bronchogenic carcinoma.
- Strong association with **smoking** (25 times risk).

Before, males>females, now incidence in female is rising because of smoking.

Pathogenesis : This type of Cancer is preceded by years of mucosal changes :

Respiratory epithelium → Squamous metaplasia → Dysplasia → Carcinoma in-situ → Invasive SqCc

- Carcinomas metastasize by lymphatic spread, while Sarcomas metastasize by hematogenous spread.

Syndrome

- Tumor cells secrete a parathyroid hormone -related protein (**PTH-rp**) leading to **hypercalcemia**.

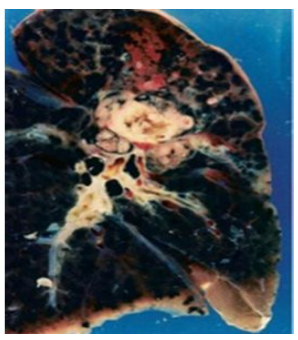
Findings

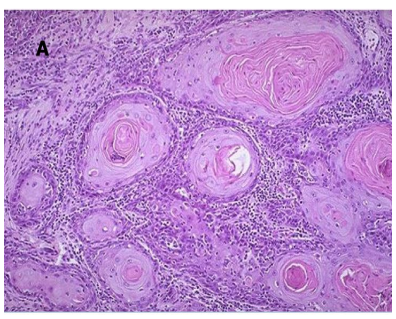
- SqCC arise in central airways (**Centrally located**), So they appear as a hilar mass.
- Frequently cavitate. (Large lesions may undergo caseous necrosis, giving rise to cavitation)
- Could present with anthracotic lymph nodes (Accumulation of carbon in the lymph nodes).
- Can present with **paraneoplastic syndromes** (manifestation of cancer causing unusual symptoms) like **hypercalcemia** and cachexia.
- Obstruction in the bronchi by a tumor could lead to recurrent pneumonia.
- Poor prognosis.

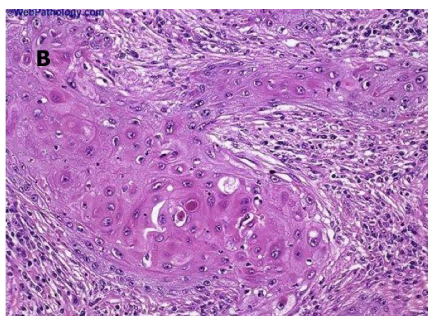
Morphology

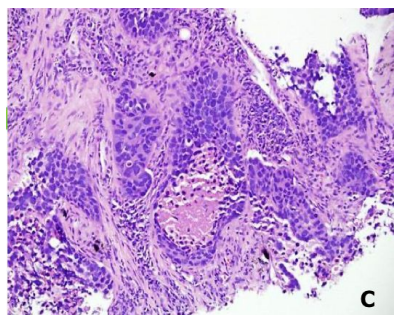
- SqCC is identified under the microscope by the presence of **keratin pearls** and intercellular bridges (Desmosomes).
- Histologically, these tumors are graded **according to degree of squamous differentiation ranging** from:

1. Well differentiated SqCC (Figure A)
2. Moderately differentiated SqCC (B)
3. Poorly differentiated SqCC (C)



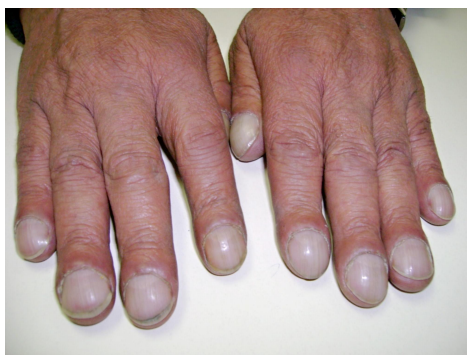


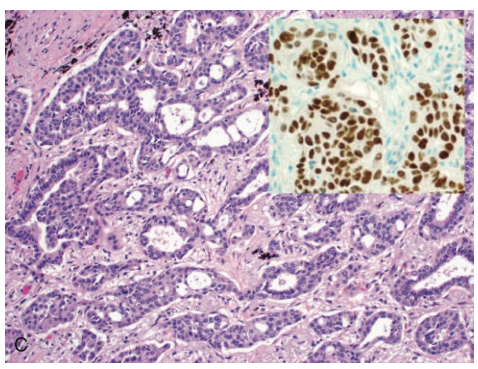




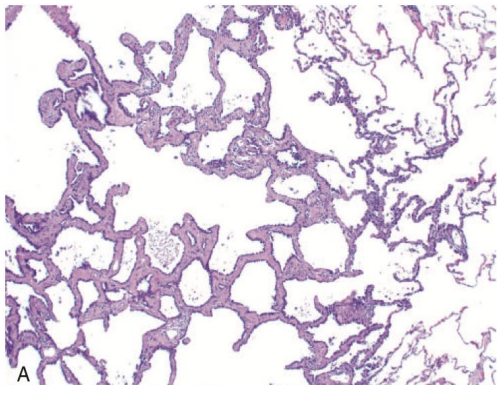
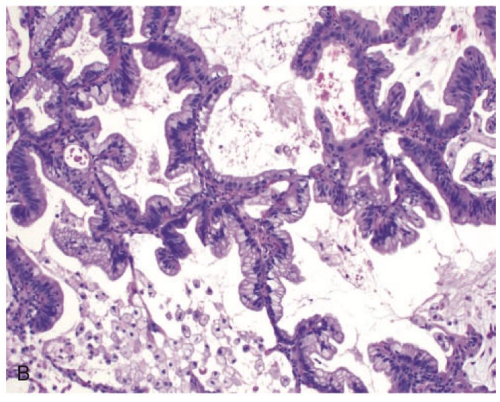
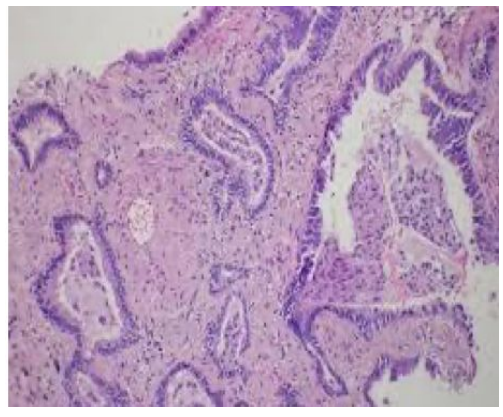
B. Adenocarcinoma

Epidemiology	• **Adenocarcinomas is now the most frequent histologic subtype** of bronchogenic carcinoma. • More common in patients under the age of 40, **women and non-smokers.** • **They do not have a clear link to smoking history**
Etiology	• 25% of the patients have a mutation in Epidermal growth factor receptor (**EGFR**) (It is a receptor tyrosine kinase that controls signal transduction pathways regulating proliferation, apoptosis, angiogenesis) • Anti EGFR can cure Adenocarcinoma if the patient has EGFR positive (not in all cases). • Some patients have mutations that activate other tyrosine kinases, including **ALK**, **ROS1**.
Findings	• They are classically **peripheral** tumors arising from the peripheral airways and alveoli (they are not always peripheral). • Rarely cavitate. • Peripheral adenocarcinomas are sometimes associated with **pulmonary scars** (from a previous pulmonary inflammation/infection) and therefore is also referred to as **scar carcinoma.** • Tend to metastasize widely at early stage. • Associated with hypertrophic pulmonary osteoarthropathy "**Clubbing of the fingers"**
Morphology	• The hallmark of adenocarcinomas is the tendency to **form glands** that may or may not produce mucin. • Well differentiated cell (Grade I) produce more mucus, while poorly differentiated cells (Grade III) produce less mucus.





Adenocarcinoma

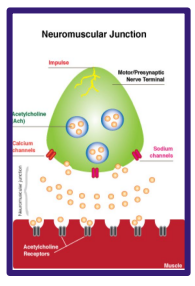
Adenocarcinoma precursor lesions		
Atypical adenomatous hyperplasia	**Adenocarcinoma in-Situ (AIS)**	**Minimally invasive Adenocarcinoma (MIA)**
is a small lesion (≤5 mm) characterized by dysplastic pneumocytes lining alveolar walls that are mildly **fibrotic**.	• Formerly called **bronchoalveolar carcinoma** • is a lesion that is less than 3 cm and is composed entirely of dysplastic cells **growing along preexisting alveolar septae.** • no growth patterns other than lepidic[1]. i.e It has lipidic pattern, it is also peripheral, it looks like a benign tumor. • **no feature of necrosis or invasion.** • poorly differentiated: because it can't maintain a special type	≤3 cm describes small solitary adenocarcinomas with either pure lepidic growth or predominant lepidic growth with ≤5 mm of stromal invasion. (Stromal invasion of the alveolar wall septae)
		

1/ lepidic pattern is defined as neoplastic cells lining the alveolar wall with no architectural disruption.

C. Small cell carcinoma

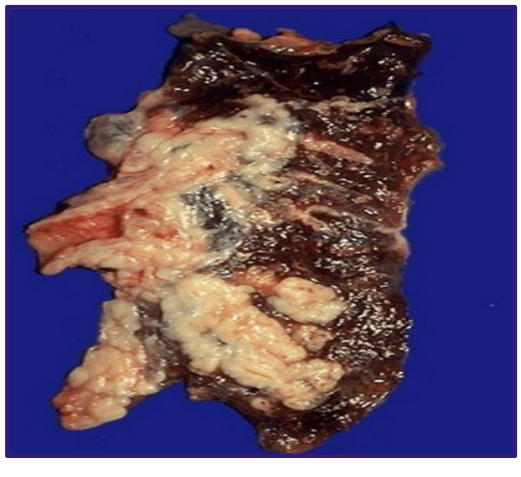
Epidemiology	SCLC are a type neuroendocrine tumors **arising from neuroendocrine cells.** **More common in men.**
	Strongly associated with cigarette smoking. 95% of patients are smokers
Treatment	**Chemotherapy** responsive least likely from to be cured by surgery; usually already metastatic at diagnosis , recur invariably
Prognosis	**Highly malignant and aggressive tumor**, poor prognosis, rarely resectable .
Findings	**Centrally located perihilar mass with early metastases** (Early involvement of the hilar and mediastinal nodes) Ability to secrete a host of polypeptide **hormones like ACTH (leading to Cushing's syndrome), antidiuretic hormone** (ADH), calcitonin, gastrin-releasing peptide and chromogranin.
Syndromes	**It may be associated with paraneoplastic syndrome e.g. Cushing's and Eaton-Lambert syndrome**

Eaton-Lambert syndrome

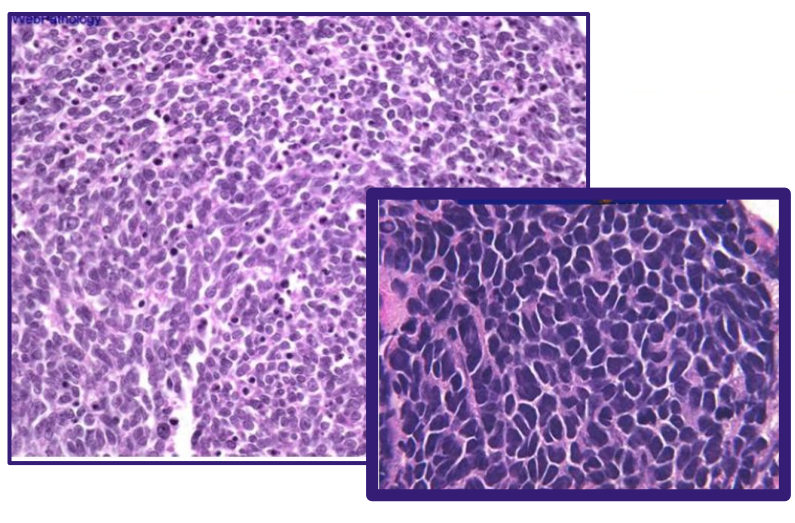


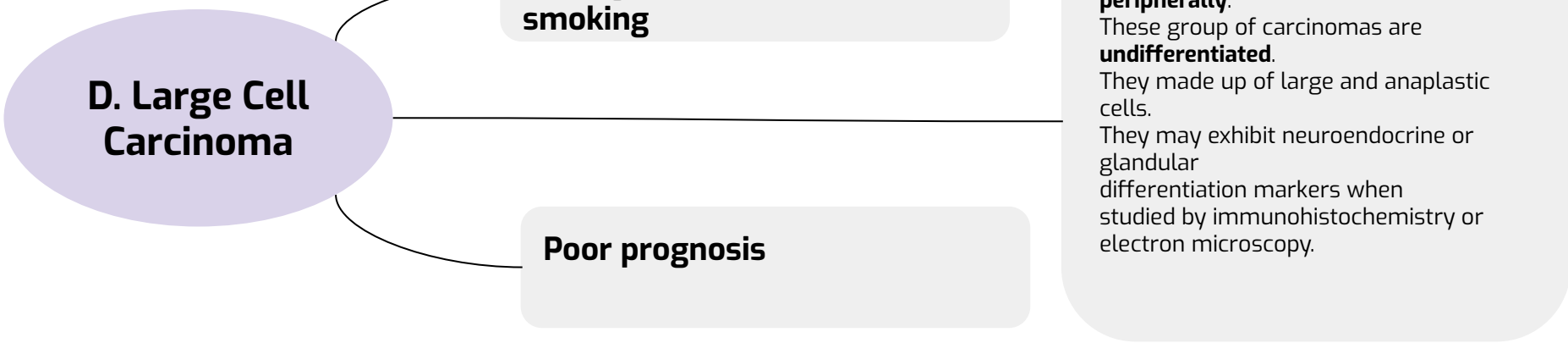
Not important , you only have to know it associates with SCC

1) is an autoimmune disease
2) a disease in which the immune system attacks the body's own tissues.
3) The attack occurs at the connection between nerve and muscle (the neuromuscular junction)
4) and interferes with the ability of nerve cells to send signals to muscle cells.



- Microscopically composed of small, dark, round to oval, **lymphocyte-like cells** with little cytoplasm.
- Electron microscopy: dense-core neurosecretory granules.





Molecular genetics in lung cancer

a. Most common oncogenes—
KRAS, MYC family, HER-2/neu, BCL-2, EGFR, ROS1 and ALK.

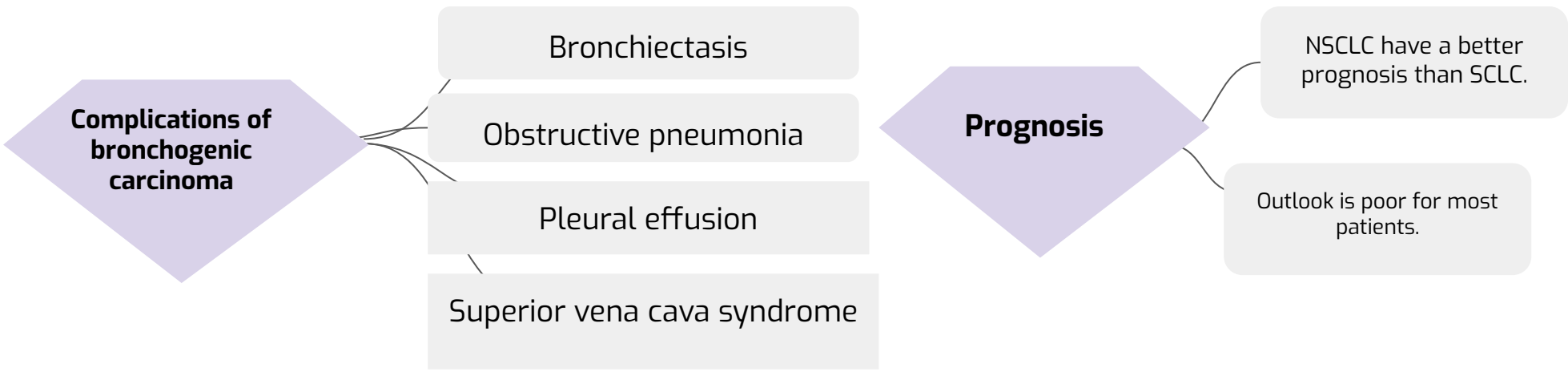
(epidermal growth factor receptor found in some cases of pulmonary adenocarcinoma, if certain mutation is positive, will respond to anti-tyrosin kinase) (very important)

so on all cases of adenocarcinoma and SCC we do EGFR and if negative; ALK and ROS1 are done.

b. Most common suppressor genes—p53 (most common), RB1 and p16

Clinical features of bronchogenic carcinoma

- Can be silent or insidious lesions.(asymptomatic)
- chronic cough and expectoration, hemoptysis,and bronchial obstruction, often with atelectasis.
- Hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion.
- Symptoms due to metastatic spread.



Clinical features: may also be manifest by the following

Important

Pancoast tumor (superior sulcus tumor)	Horner syndrome	Superior vena cava syndrome	Others
Apical neoplasms may invade the brachial sympathetic plexus to cause severe pain, numbness and weakness in the distribution of the ulnar nerve.(in the apex of the lung) The combination of clinical findings is known as **Pancoast syndrome.**	invasion of the cervical thoracic sympathetic nerves and it leads to ipsilateral enophthalmos, miosis, ptosis, and facial anhidrosis	invasion leads to obstruction of venous drainage which leads to dilation of veins in the upper part of the chest and neck resulting in swelling and cyanosis of the face, neck, and upper extremities.	**-Hoarseness from recurrent laryngeal nerve paralysis.** **-Pleural effusion, often bloody with high fibrin and protein contents.** **Paraneoplastic syndrome.**
Pancoast tumor is often accompanied by destruction of the first and second ribs and thoracic vertebrae lead to (with invasion of Cervical Thoracic sympathetic nerves in addition to numbness and weakness of the hand, so it **coexist with ipsilateral enophthalmos**) **Pancoast (Horner) syndrome**			

Paraneoplastic syndrome

- **Paraneoplastic syndromes** of lung cancer, are extrapulmonary, remote effects of tumors. 3% to 10% of lung cancers develop paraneoplastic syndromes. (caused by SQCC but unrelated) Lead to: hypercalcemia + cachexia (tumor secretes proteins similar in structure and function to PTH

1. **Small cell lung carcinoma**
   ACTH (leading to Cushing's syndrome)
   ADH (water retention and hyponatremia)
2. **Adenocarcinoma**
   can lead to hematologic manifestations (Problems in
3. **Sq.c.c**
   may secrete parathyroid hormone-like peptide and prostaglandin E that lead to hypercalcemia
4. **Carcinoid tumor**
   produce serotonin and bradykinin leading to carcinoid syndrome (flushing, wheezing, diarrhea, and cardiac valvular lesions)

Other endocrine syndromes associated with primary lung carcinomas e.g. gonadotropin production leading to gynecomastia, calcitonin production leading to hypocalcemia, hyperglycemia, thyrotoxicosis, and skin pigmentation

E. Carcinoid Tumors

Epidemiology

- **Carcinoid tumors of the lung are neuroendocrine neoplasms.** Very well differentiated neuroendocrine tumor (localized and can be excised)
- These neoplasms account for 2% of all primary lung cancers,
- It shows no sex predilection, and are not related to cigarette smoking or other environmental factor.
- Usually seen in adults

Syndrome

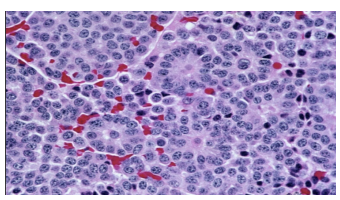
- **Tumor cells** produce serotonin and bradykinin leading to carcinoid syndrome . carcinoid syndrome (vasoactive amines—>palpitations, diarrhea, abdominal pain, heart changes)

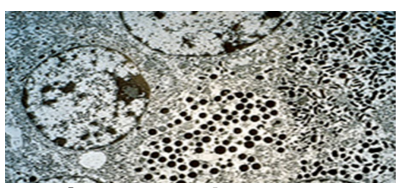
Findings

- Can be **central or peripheral** in location.
- **Tumor cells produce serotonin and bradykinin leading to carcinoid syndrome**
- Can occur in patients with Multiple Endocrine Neoplasia (MEN-I) hereditary
- **Low malignancy**, Often resectable and curable.
- Spreads by direct extension into adjacent tissue

Morphology

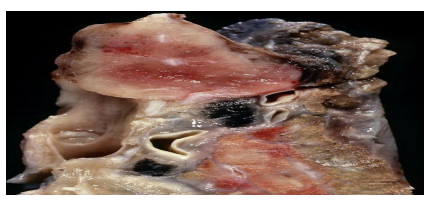
Microscopically :(**it's for your knowledge to answer the cases just understand it)** uniform cuboidal cells , few mitoses and little or no anaplasia.





Electron microscopy

dense-core neurosecretory granules



carcinoid in central portion

Spread of bronchogenic carcinoma:

Direct

1-May invade the brachial or cervical sympathetic plexus (Horner's Syndrome).
2-May extend directly into the esophagus, producing obstruction, sometimes complicated by a fistula.
3-Phrenic nerve invasion usually causes diaphragmatic paralysis
4-Extend into the pericardial or pleural spaces. infiltrating the superior vena cava.

Lymphatic spread

a. successive chains of nodes (scalene nodes)
b. involvement of the supraclavicular node (Virchow's node)

Distant metastasis

Distant metastasis to liver (30-50%), **adrenals** (>50%), brain (20%) and bone (20%).

F. Mesothelioma

Epidemiology	**Malignant tumor of mesothelial cells lining the pleura**
	The average age of patients with mesothelioma is 60 years. Smoking is not related to mesothelioma Most patients (70%) have a history of **exposure to asbestos**
Treatment	Treatment is largely ineffective
Prognosis	**prognosis is poor:** few patients survive longer than 18 months after diagnosis, **Highly** malignant neoplasm.
Findings	Pleural mesotheliomas tend to **spread locally** within the chest cavity, invading and compressing major structures. Metastases can occur to the **lung parenchyma** and mediastinal lymph nodes, as well as to extrathoracic sites e.g. **liver**, **bones**, peritoneum etc. ➔ malignant tumor of the pleura caused by asbestos.

Carcinoma metastatic to the lung

- Pulmonary Metastases are **More Common** than Primary Lung Tumors
- Metastatic tumors in the lung are typically **multiple and circumscribed.** When large nodules are seen in the lungs radiologically, they are called cannon ball metastases .
- The common primary sites are the **breast**, **stomach**, **pancreas**, and **colon**.

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Quiz

1- 52-year-old woman presents with a 1-year history of upper truncal obesity and moderate depression. Physical examination shows hirsutism and moon facies. Endocrinologic studies reveal hypokalemia, high plasma corticotropin levels, and increased concentrations of serum and urine cortisol. CT scan of the thorax demonstrates a hilar mass. A transbronchial lung biopsy is shown in the image. Electron microscopy discloses neuroendocrine granules within the cytoplasm of some tumor cells. What is the appropriate diagnosis?			
a- small cell carcinoma	b- large cell carcinoma	c- adenocarcinoma	d- squamous cell carcinoma
2-55-year-old man presents with increasing chest pain, bloody sputum, and weight loss over the past 3 months. A high resolution CT scan reveals a mass circumscribing the right main bronchus, extending into its lumen. Histologic examination of an open-lung biopsy,. Electron microscopy shows numerous neuroendocrine granules within tumor cells. What is the appropriate diagnosis?			
a- carcinoid tumor	b- small cell carcinoma	c- adenocarcinoma	d- squamous cell carcinoma
3- a 55 years old woman has a 3-month history of chronic cough. She denies smoking, but admits a 5 Kg weight loss. She had recurrent infections over the past 2 years which produced cavitation. A chest X-ray show a peripheral lesion near the previous site of infection. What is the most likely diagnosis?			
a- large cell carcinoma	b- squamous cell carcinoma	c- adenocarcinoma	d- small cell carcinoma
4- A 60 years old man has a persistent cough and flecks of blood in his sputum. He admits a 9 Kg weight loss in the past 4 months and a smoking history. Physical examination shows right eyelid lag,digital clubbing and hypercalcemia. A chest X-ray show peribronchial mass with central cavitation in right lung. What is the most likely diagnosis?			
a- Squamous cell carcinoma	b- carcinoid tumor	c- small cell carcinoma	d- mesothelioma
5- 58-year-old man presents with a long history of persistent cough, chest pain, and recurrent pneumonia. He denies smoking or consuming alcohol. The patient subsequently dies of sepsis. Autopsy reveals malignant cells that diffusely infiltrate the lung parenchyma. Histopathologic examination of the lung shows well-differentiated, mucus-producing, columnar neoplastic cells lining the alveolar spaces (shown in the image). Neoplastic cells are not found in any other organ. What is the most likely diagnosis?			
a- Bronchioloalveolar carcinoma	b- Carcinoid tumor	c- Large cell carcinoma	d- Mesothelioma
6- Which of these Adenocarcinomas is identified by lipidic pattern, looking like a benign tumor, and having no feature of necrosis or invasion. Also it is poorly differentiated.			
a- Atypical adenomatous hyperplasia	b- Adenocarcinoma in-Situ (AIS)	C- Minimally invasive Adenocarcinoma (MIA)	d- Both A&B

ANSWER KEY:

1.A
2.A
3.C
4.A
5.A
6.B

Squamous cell carcinoma
- Associated with smoking.
- Paraneoplastic parathyroid-like actions.
- Keratin pearls are seen histologically.

Pancoast's tumour
Results in Horner's syndrome, a triad of:
1 Miosis.
2 Ptosis.
3 Anhidrosis.

Adenocarcinoma
- NOT associated with smoking.
- More common in women.
- Associated with hypertrophic osteoarthropathy.
- Mucin-positive staining seen on histology.

Apex

Central location

MAP 2.6 Lung Cancer

Peripheral location

Pleura

Small cell carcinoma
- Also know as oat cell carcinoma.
- Very aggressive, therefore treat solely with chemotherapy regime.
- Adrenocorticotrophic hormone (ACTH) and antidiuretic hormone (ADH) are generated ectopically.
- Associated with Lambert–Eaton syndrome.
- Kulchitsky cells are seen histologically.
- Non small cell carcinomas (NSCC) are any epithelial derived lung cancers that are not small cell carcinoma (SCC). They are relatively insensitive to chemotherapy.

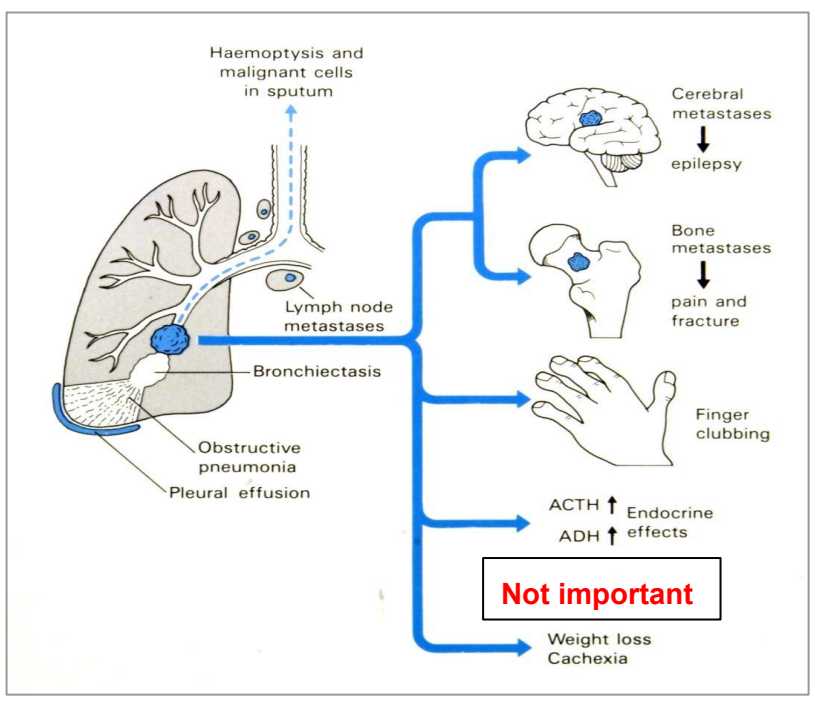
Mesothelioma
- Associated with asbestosis.
- Psammoma bodies are seen histologically.

Large cell carcinoma
- Patient is likely to have a poor outcome.
- Lack light microscopic features of other tumour types.
- Larger sized anaplastic cells.
- High cytoplasmic-to-nuclear size ratio.
- Treated by surgical excision of tumour.

SUMMARY

CARCINOMA OF THE LUNG

- The three major histologic subtypes are adenocarcinoma (most common), squamous cell carcinoma, and small cell carcinoma, each of which is clinically and genetically distinct. Adenocarcinomas are the most common cancers overall and are especially common in women and in nonsmokers.



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