PATHOLOGY TEAM 436

MEDICINE 436 KING SAUD UNIVERSITY

اللهم لا سهلًا إلا ما جعلته سهلاً وأنت تجعل الحزن إن شئت سهلاً

Tumors of the lung

Editing file

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Doctor notes: green
Important : red
Extra explanation grey

Objectives:

1-Understand the incidence, age group of affected patients and predisposing factors of bronchogenic carcinoma.
2- Is aware of the new classification of bronchogenic carcinoma which include ; squamous carcinoma, adenocarcinoma, small cell and large cell (anaplastic) carcinomas
3- 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)
4- Have a basic knowledge about neuroendocrine tumours with special emphasis on small cell carcinoma and bronchial carcinoid.
5- Is aware that the lung is a frequent site for metastatic neoplasms.

Introduction:

Most lung tumors are malignant.

-Primary lung cancer is a common disease BUT **metastatic tumors** are more common than the primary tumors.

-The most common benign lesions are hamartoma it is abnormal mass of tissue consist of different and abnormal tissues which are present in variable proportion and it is indigenous to the site where they arise from.
Sometimes they call it (leave me alone lesions)

Epidemiology

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.

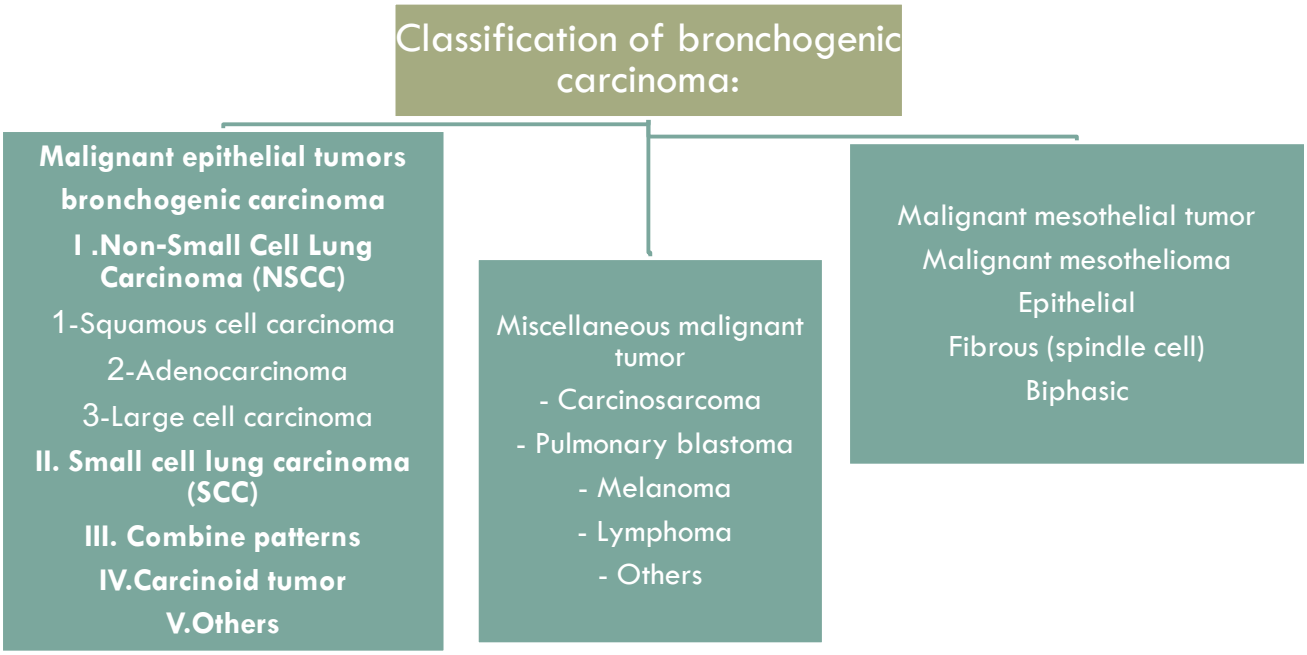
-Adenocarcinoma (38%)

-Squamous cell carcinoma (20%)

-Small cell carcinoma (14%)

-Large cell carcinoma (3%)

-Other (25%)



Classification of Malignant epithelial tumors of lung

I. Non-Small Cell Lung Carcinoma (NSCC)
1-Squamous cell carcinoma (SqCC)
2- Adenocarcinoma, including bronchioloalveolar carcinoma
3- Large cell carcinoma
II. Small cell lung carcinoma (SCC)
III. Combine patterns
- Most frequent patterns:
- Mixed squamous cell ca and adenocarcinoma.
- Mixed squamous cell ca and SCC.
IV. Carcinoid tumors
V. Others

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

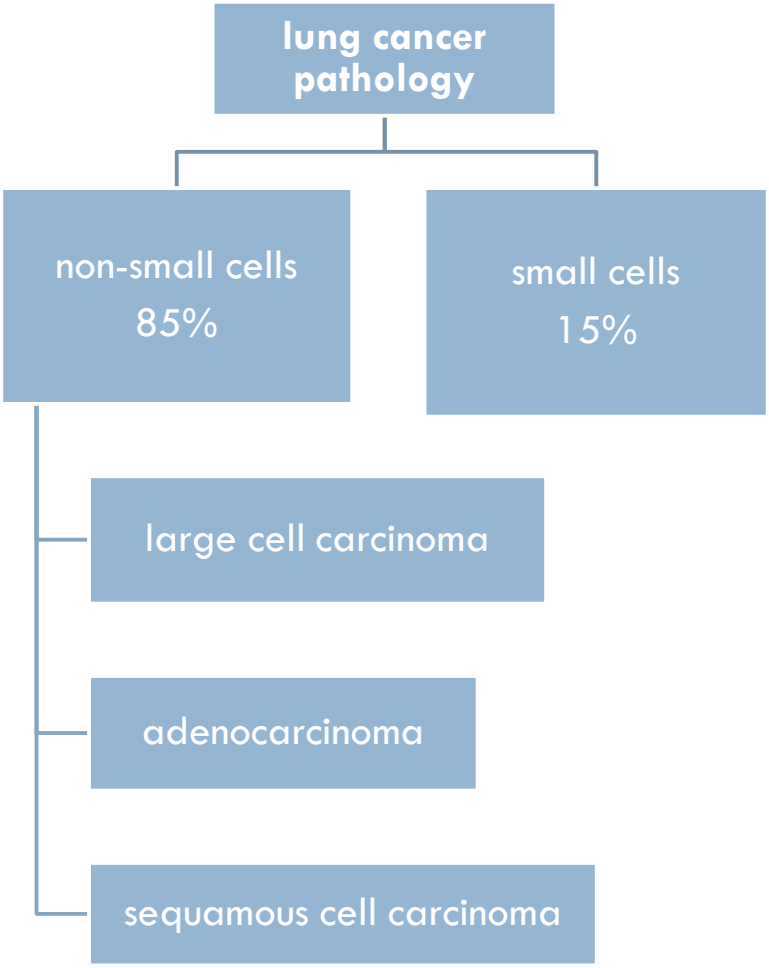
Bronchogenic carcinoma:

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

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

-For therapeutic purposes, bronchogenic carcinoma are classified into:
1- Non- Small cell lung carcinoma (NSCC) which includes squamous cell, adenocarcinomas, and large-cell carcinomas.

2- Small cell lung carcinoma (SCC)



Bronchogenic carcinoma

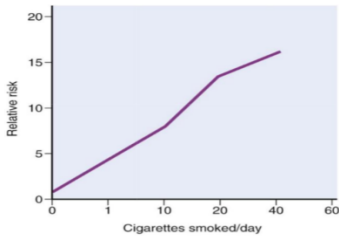
•It is important to differentiated NSCC from SCC because treatment are different

NSCC therapy	SCC therapy
1-**Surgical** - offers the best chance for curing. 2-Radiation - controls local disease. Radiation therapy is most commonly used to palliate symptoms. 3-Chemotherapy – not effective.	Chemotherapy is very effective because small cell carcinomas are highly responsive to chemotherapy

Predisposing factors of bronchogenic carcinoma

1- **Tobacco smoking:** (About 90% of lung cancers occur in active smokers or those who stopped recently).

- 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. (Adenocarcinoma usually associated with scarring)
- Is directly proportional to the: **1-** number of cigarettes smoked daily **2-**the number of years of smoking.
- Cessation of cigarette smoking for at least 15 years brings the risk down. (but it may never return to baseline levels)
- Passive smoking increases the risk to approximately **twice** than nonsmokers. (Passive smoking= second hand smoke = proximity to cigarette 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.



Study: "If woman smoke like men, they will die like men"

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.

2- **Radiation:** All types of radiation may be carcinogenic and increase the risk of developing lung cancer. **Tradium** and **uranium** workers are at risk. (especially CT scan)

3- **Asbestos:** increased incidence of cancer with asbestos exposure, especially in combination with cigarette smoking. (Heavy smokers exposed to asbestos have an approximately 55 times greater risk for development of lung cancer than that for nonsmokers not exposed to asbestos.)

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

5- **Air pollution:** May play some role in increased incidence. Indoor air pollution especially by radon.

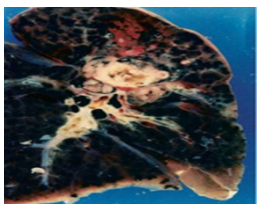
6- **Scarring:** sometimes old infarcts, wounds, scar, granulomatous infections are associated with adenocarcinoma.

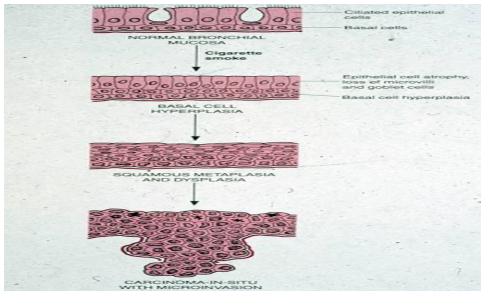
Precursor Lesions

- Three types of precursor epithelial lesions are recognized:
  1- **Squamous dysplasia** and **carcinoma in situ** can **lead to:**
  Squamous cell carcinoma
  2- **Atypical adenomatous hyperplasia** can **lead to:**
  Adenocarcinoma
  3- 3- Diffuse **idiopathic pulmonary neuroendocrine** cell **hyperplasia** can **lead to:**
  Neuroendocrine tumors
- It should be noted that the term "precursor" does not imply that progression to invasion will occur in all cases.

Squamous cell carcinoma

- (It's look like squamous has ability to produce **certain** and the cell have **desmosome** "junction between squamous cell")
- Patient may present with **unresolved pneumonia,**[1] very sever **cough** and **hemoptysis** and compline from **extremely Wight loss.**
- Second most common bronchogenic carcinoma.
- Strong association with smoking (25 times risk).
- Before Males>Females, now incidence in female rising because of smoking.
- This type of cancer is preceded by years of progressive mucosal changes of respiratory epithelium to squamous **metaplasia** (change from one type of epithelium to another) **to dysplasia** (premalignant condition characterized by presence of atypical abnormal cells) **to CA in situ to invasive SCC.**
- Sequence of events : smoking habits → irritations of bronchial mucosa → squamous metaplasia → metaplastic squamous epithelium → dysplasia
- SqCC arise in the central airways (centrally located). So they appear as a hilar mass. (usually central mass of the hilum of the lung and showing necrosis)
- Frequently **cavitate.**
- Tumor cells secrete a parathyroid hormone (PTH)- like peptide leading to hypercalcemia (hypercalcemia one of the paraneoplastic syndrome which mean the symptoms or sings not directly related to the effect of tumor but they coexist with tumor and are result with secretion of substances).
- **Poor** prognosis.



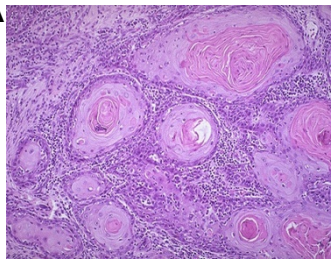


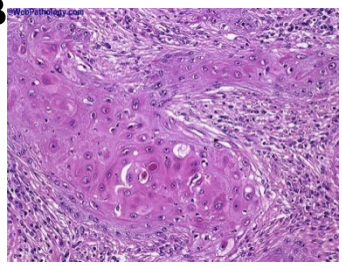
[1] ممكن يكون شيخ عمره 80 عام يصير عنده التهاب بالرئة pneumoniaوصار له 3 اشهر تروح وترجع

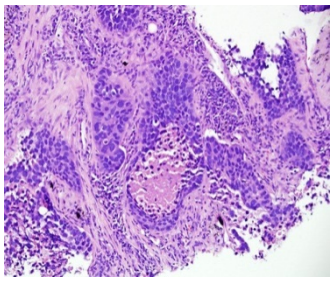
Histologically

These tumors are graded according **to degree of squamous differentiation** and tumors ranges from:

- well-differentiated squamous cell carcinoma (A)
- moderately differentiated SqCC (B) to
- poorly differentiated SqCC (C).

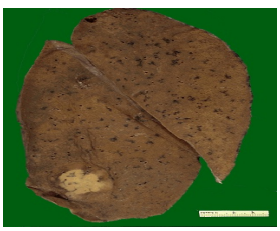
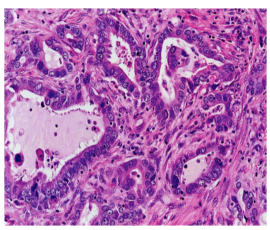
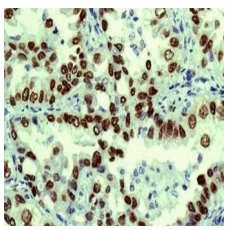
A 

B 

C 

Adenocarcinomas

- Adenocarcinomas is now **the most** frequent histologic subtype of bronchogenic carcinoma; more common in **women.**
- They do not have a clear link to smoking history
- Most often they are associated with pulmonary scars (from a previous pulmonary inflammation/infection) and therefore are also referred to as scar carcinoma.
- They are classically peripheral tumors arising from the peripheral airways and alveoli
- More common in patients under the age of 40, women and non-smokers.
- Tend to metastasize widely at early stage
- The hallmark of adenocarcinomas is the tendency to **form glands** that may or may not produce **mucin.**
- 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.
- Associated with hypertrophic pulmonary osteoarthropathy **"Clubbing of the fingers"**
- Genetically engineer therapy: Anti-EGFR drugs for e Epidermal Growth Factor Receptor mutation which is responsible for occurrence of adenocarcinoma at the 20%-25% of the cases . (A subset of adenocarcinomas, particularly those arising in nonsmoking women of Far Eastern origin, harbor activating mutations of the epidermal growth factor receptor (EGFR). Of note, these tumors are sensitive to a class of agents that inhibit EGFR signaling, although the response often is short-lived. EGFR and K-RAS mutations (in 30% of adenocarcinomas) are mutually exclusive. Other mutations occurring in 4% to 6% of adenocarcinomas **are EML4-ALK tyrosine kinase fusion genes** and c-MET tyrosine kinase gene amplifications. These abnormalities, while rare, are important because of their therapeutic implications, as they can be targeted with tyrosine kinase inhibitors. Indeed, the identification of genetic alterations producing overactive EGFR, ALK, and MET has opened up a new era of "personalized" lung cancer therapy, in which the genetics of the tumor guides the selection of drugs.)

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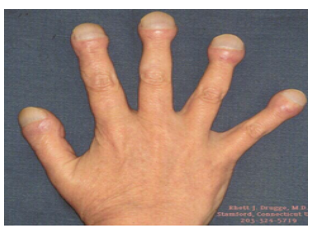
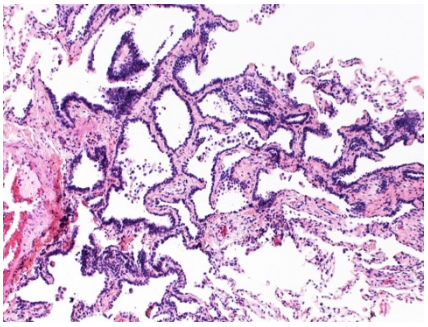


Clubbing of the fingers

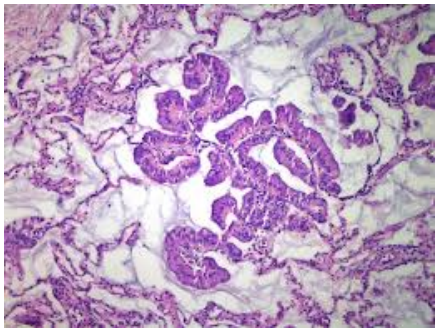
*thyroid transcription Factor

Adenocarcinoma Precursor Lesions

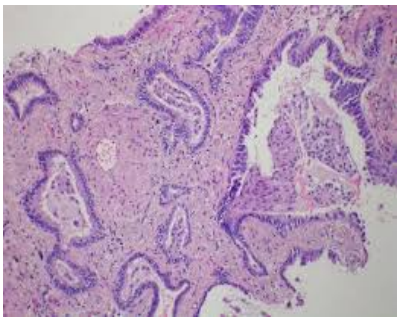
- **Atypical adenomatous hyperplasia**(not cancer but it may develop cancer) is a small lesion **(≤5 mm)** characterized by dysplastic pneumocystes' lining alveolar walls that are mildly fibrotic
- **Adenocarcinoma in situ; AIS** (growing along the alveoli lining) (formerly called bronchioloalveolar 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 and NO feature of necrosis or invasion
- **Minimally invasive adenocarcinoma of lung (MIA)** ≤3 cm, describes small solitary adenocarcinomas with either pure lepidic growth or predominant lepidic growth with ≤5 mm of stromal invasion. (minimally invasive adenocarcinoma (tumor less than 3 cm and invasive component measuring 5 mm or less), and invasive adenocarcinoma (tumor of any size that has invaded to depths greater than 5 mm)) (lepidic pattern is when it follows the basement membrane of the alveoli)



Atypical adenomatous hyperplasia



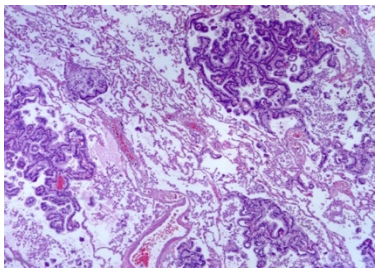
Adenocarcinoma in situ (formerly called bronchioloalveolar carcinoma)

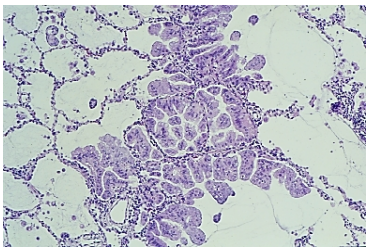


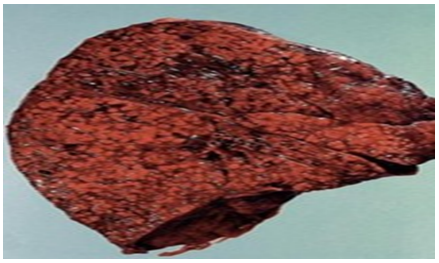
Minimally invasive adenocarcinoma of lung

Adenocarcinoma in situ (formerly called bronchioloalveolar CA)

- referred to as adenocarcinoma in situ according to the new classification of lung cancers
- malignant cells grow along alveolar septa







Large Cell Carcinoma (Anaplastic Carcinoma of the lung):

• Frequency: 10 %.

• Strongly associated with smoking.

• Large-cell carcinoma is usually located peripherally. These group of carcinomas are **undifferentiated.** They made up of large and **anaplastic cells**. They may exhibit neuroendocrine or glandular differentiation markers when studied by **immunohistochemistry** or **electron microscopy.**

• Poor prognosis.

Small cell carcinomas (Oat cells carcinoma of lung, Poorly differentiated neuroendocrine carcinoma of lung).

• SCLC are a type neuroendocrine tumors arising from neuroendocrine cells. More common in **men.**

• Highly malignant and aggressive tumor, poor prognosis, rarely resectable(removed).

• Strongly associated with cigarette smoking. 95% of patients are smokers.

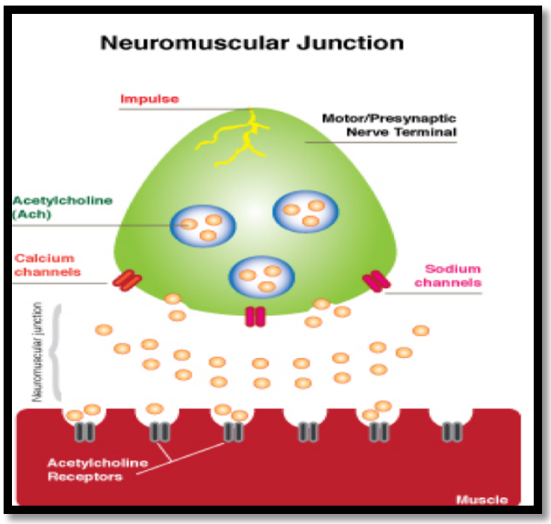
• Centrally located perihilar mass with early metastases (Early involvement of the hilar and mediastinal nodes).

• Chemotherapy responsive. Treated by aggressive chemotherapy, no Anti genes to treat this tumor.

• Least likely form to be cured by surgery; usually already metastatic at diagnosis

• Ability to secrete a host of polypeptide hormones like **AdrenoCorticoTropic hormone** ACTH, antidiuretic hormone (ADH), calcitonin, gastrin-releasing peptide and chromogranin.

• It may be associated with paraneoplastic syndrome, Cushing's (by secreting ectopic ACTH), and Eaton-Lambert syndrome.



Eaton-Lambert syndrome

•An autoimmune disease.

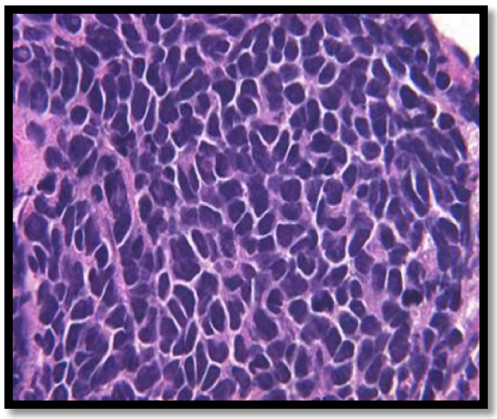
• A disease in which the immune system attacks the body's own tissues.

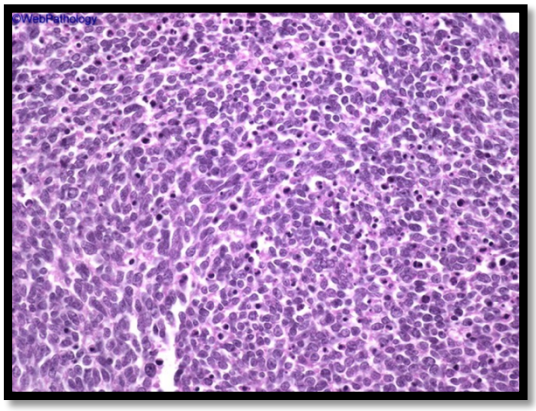
• The attack occurs at the connection between nerve and muscle (the neuromuscular junction) and interferes with the ability of nerve cells to send signals to muscle cells.

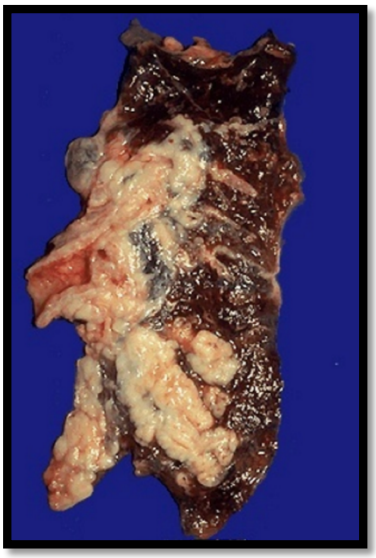
Small cell carcinomas Microscopically

• Microscopically composed of small, dark, round to oval, lymphocyte-like cells with little cytoplasm.

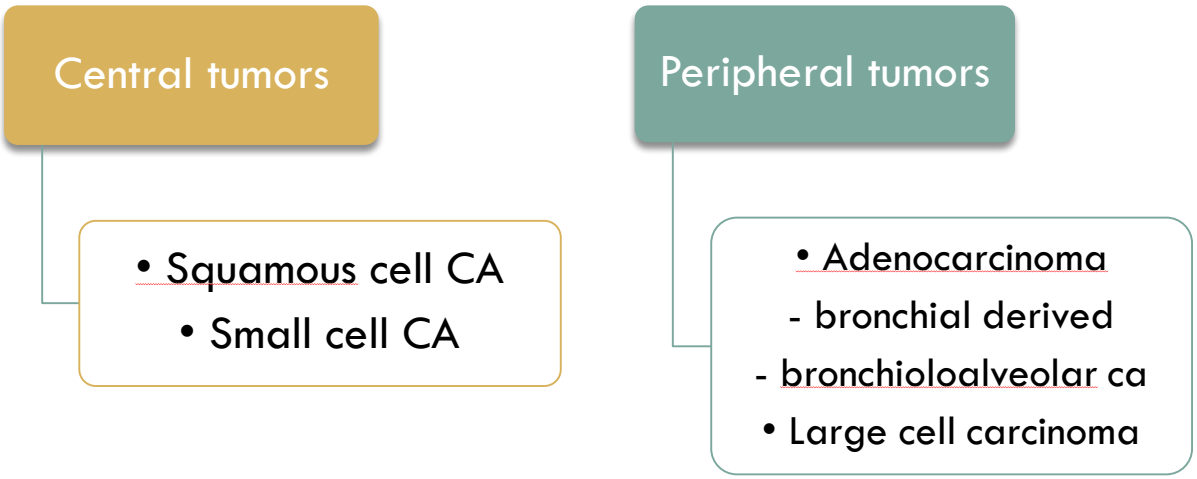
• Electron microscopy: dense-core neurosecretory granules.







Bronchogenic carcinoma site



Molecular genetics in lung cancer

a. Most common oncogenes: KRAS, MYC family, HER-2/neu, BCL-2, EGFR

(epidermal growth factor receptor found in pulmonary adenocarcinoma, if certain mutation is positive, will respond to anti-tyrosin kinase for ALK gene).

لما يكون عند شخص مشكلة بال EGFR gene نعالجه بال Anti EGFR gene في 20%-25% منAdenocarcinoma حالات

لكن لما يكون هذا الشخص عنده مشكلة بال ALK gene نعالجة بال Anti-tyrosin kinase

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

Most of the cancers have abnormalities in the short arm of chromosome 3p. The short arm of the chromosome has tumor suppressors that become inactivated.

(Inactivation of the putative tumor suppressor genes located on the short arm of chromosome 3 (3p) is a very early event, whereas TP53 mutations or activation of the KRAS oncogene occurs relatively late. More important, it seems that certain genetic changes, such as loss of chromosomal material on 3p, can be found even in benign bronchial epithelium of persons with lung cancer.)

Clinical features of bronchogenic carcinoma

• Can be silent or insidious lesions

• Chronic/severe cough and expectoration[2], hemoptysis, and bronchial obstruction, often with atelectasis[3], bloody sputum, unexplained fever.

• Hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion(bloody), pleuritic pain.

[2] Sputum
[3] Complete or partial collapse of a lung or lobe of a lung

• Symptoms due to direct or metastatic spread.

• Unresolving bronchopneumonia (may grow staphylococcus aureus or moraxella catarrhalis (in exacerbation of chronic bronchitis) and haemophilus influenza.

• Unresolved pneumonia because, usually the neoplasm causes obstruction, and obstruction predisposes to infection. Ex. 80 years old has recurrent lung inflammation for 3 months, you must ask yourself what is behind this bronchopneumonia? An obstructive lesion, usually caused by malignant neoplasm.

• Anorexia, cachexia (paraneoplastic syndrome, caused by TNF).

• Metastases to the lung from malignant tumors elsewhere, is more common than primary lung tumors. Applies to liver too. (One mass, primary. Cannon ball, secondary4).(Important notes)

Clinical Feature	Pathologic Basis
Cough (50%-75%)	Involvement of central airways
Hemoptysis (25%-50%)	Hemorrhage from tumor in airway
Chest pain (20%)	Extension of tumor into mediastinum, pleura wall
Pneumonia, abscess, lobar collapse	Airway obstruction by tumor
Lipoid pneumonia	Tumor obstruction; accumulation of cellular l foamy macrophages
Pleural effusion	Tumor spread into pleura
Hoarseness	Recurrent laryngeal nerve invasion
Dysphagia	Esophageal invasion
Diaphragm paralysis	Phrenic nerve invasion
Rib destruction	Chest wall invasion
SVC syndrome	SVC compression by tumor
Horner syndrome	Sympathetic ganglia invasion
Pericarditis, tamponade	Pericardial involvement

4 تنتشر مثل قذائف المدفع

Bronchogenic CA may manifest by the following syndromes:

- **Superior vena cava syndrome:** 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

- **Pancoast tumor (superior sulcus tumor):** Apical neoplasms may invade the brachial sympathetic plexus to cause severe pain, numbness and weakness in the distribution of the ulnar nerve.

- **Pancoast syndrome:** Known as the combination of clinical findings.
  Pancoast tumor is often accompanied by **destruction** of the first and second ribs and thoracic vertebrae. It often coexists with **Horner syndrome** (invasion of the cervical thoracic sympathetic nerves and it leads **to ipsilateral enophthalmos, miosis, ptosis, and facial anhidrosis**[5].)

These are symptoms of Horner syndrome caused by a Pancoast tumor which is a bronchogenic carcinoma in **the apex in the upper lobe** of the lung that leads to invasion and compression of sympathetic nerves within the **brachial plexus** and affect the parasympathetic neurological plexuses.

- **Paraneoplastic syndrome**

When Symptoms and signs maybe not directly related to the tumors but they coexist with the tumor and are a result of secretion of substances by the tumor. It is found in lung cancer patients or caused by metastasis of another type of cancer.

Cachexia, finger clubbing, polymyositis, hypercalcemia they all are paraneoplastic syndromes.

Extrapulmonary, remote effects of tumors.
3% to 10% of lung cancers develop paraneoplastic syndrome.

a) **Small cell carcinomas**

ACTH AdrenoCorticoTrophic Hormone, AKA ectopic ACTH (leading to Cushing's syndrome with a moon shaped facial feature[6])
ADH AntiDiuretic Hormone, (water retention and hyponatremia)

b) **Carcinoid tumors**

(secrete vasoactive amines) produce serotonin and bradykinin leading to **carcinoid syndrome** (flushing, wheezing, diarrhea, and cardiac valvular lesions)

c) **Squamous cell carcinomas**

may secrete **parathyroid hormone-like** peptide and prostaglandin E that lead to hypercalcemia

d) **Adenocarcinomas**

can lead to **hematologic manifestations.**

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

[5] نصف وجهه لا يتعرق
[6] وجهه مثل البدر مدور ومتورم

Complications of bronchogenic carcinoma:

1. Bronchiectasis
2. Obstructive pneumonia
3. Pleural effusion
4. Metastasis

Prognosis:

NSCLC have a **better** prognosis than SCLC. Outlook is poor for most patients.

Spread of bronchogenic carcinoma:

A. Direct extension into:

1. The **pericardial or pleural** spaces.
2. A tumor may extend directly into the **esophagus,** producing obstruction, sometimes complicated by a fistula.
3. **Phrenic nerve** invasion usually causes **diaphragmatic paralysis**
4. May invade the **brachial or cervical sympathetic plexus**
5. Infiltrate the **superior vena cava.**

B. Lymphatic spread.

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

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

Carcinoid Tumor:

Carcinoid tumors of the lung are neuroendocrine neoplasms.

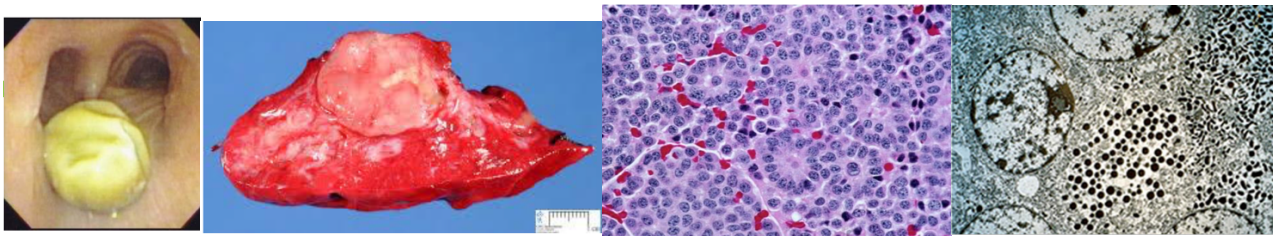
1. (Well differentiated) neuroendocrine tumor >>(Typical Carcinoid Tumor)(Low-grade)
   in classical carcinoid form it produces **endobronchial growth** so for further investigations we take a bronchial biopsy. So according to the lesions place and characteristic we change the behavior of investigations.
2. (Moderately differentiated) neuroendocrine tumor >>(Atypical Carcinoid tumor)(intermediate-grade)
3. (Poorly differentiated) neuroendocrine tumor >>(Small cell carcinoma)

- These neoplasms account for 2% of all primary lung cancers.
- It shows NO sex predilection, and are NOT related to cigarette smoking or another environmental factor.
- Usually seen in adults
- Can be **central or peripheral** in location.
- Tumor cells produce **serotonin** and **bradykinin** leading to carcinoid syndrome.

Carcinoid syndrome is **symptoms** present in patients with carcinoid tumor which is a **mass lesion**. Symptoms can be: abdominal pain, diarrhea, flushing, cyanosis… due to the vasoactive amines (serotonin...)

- Can occur in patients with Multiple Endocrine Neoplasia **(MEN-I)**

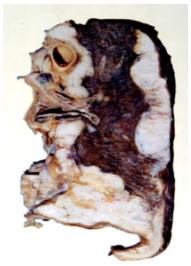
Morphology of typical carcinoid tumors



- **Composed of: uniform cuboidal cells** that have regular round nuclei with few mitoses and little or no anaplasia.
- **Electron microscopy:** dense-core **neurosecretory granules**
- **Prognosis:**

Low malignancy, Often resectable (able to be removed) and curable. Spreads by direct extension into adjacent tissue

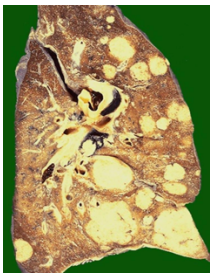
Mesothelioma:



- Malignant tumor of mesothelial cells lining the pleura.
- Highly malignant neoplasm
- Most patients (70%) have a history of exposure to asbestos.
- Smoking is not related to mesothelioma.
- The average age of patients with mesothelioma is 60 years.
- 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.
- Treatment is largely ineffective and **prognosis is poor**: few patients survive longer than 18 months after diagnosis

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.



Thank you

اللهم إني استودعتك ما قرأت وما حفظت فرده إلي وقت حاجتي

Girls

Leader:

Munirah aldofyan

Members :

1- **Aldanah Almuteb**

2- **Muneerah Alzayed**

3- **Ghada Alhadlaq**

4- **Amal AlShaibi**