Team 435

PATHOLOGY

As a doctor you should know what can threaten your patient's life
should know what makes your patient suffers from pain

That's why you study pathology

Lecture 6

Lecture Six: (Tumors of the Lung)

Objectives:

A. Understand the incidence, age group of affected patients and predisposing factors of bronchogenic carcinoma. □
B. Is aware of the classification of bronchogenic carcinoma, which include: squamous carcinoma, adenocarcinoma, small cell and large cell (anaplastic) carcinomas. □
C. Understands the clinical features and gross pathology of bronchogenic carcinoma.
D. Have a basic knowledge about neuroendocrine tumors with special emphasis on small cell carcinoma □and bronchial carcinoid. □
E. Is aware that the lung is a frequent site for metastatic neoplasms. □

Contents:

1. Bronchogenic carcinoma: aetiology, epidemiology, clinical features including superior Vena Cava syndrome, Pancoast tumor, hoarseness, pleural effusion and paraneoplastic endocrine syndromes.
2. Types, location and clinicopathological characteristics of squamous cell carcinoma, adenocarcinoma, bronchioloalveolar carcinoma, small cell carcinoma, large cell carcinoma, carcinoid tumor and metastatic carcinoma of the lung.
3. Primary and secondary tumors of the pleura.

Lung tumors:

Note: You are expected to recall many information from the neoplasia lectures taken in the foundation block, we will remind you of some the prominent ones only.

Tumors of the lung can be *benign* or *malignant*. Most tumors of the lung are malignant and can be either primary (originates from the lung) or secondary (metastatic).

Most malignant tumors found in the lung are secondary (metastatic) because the lung is a highly vascularized area; when we have multiple masses in the lung they are called cannonballs (as if someone was shooting a wall with balls). Benign tumors on the other hand are rare and usually are found incidentally[1].

With that said; if a patient comes up to you and you suspect that he has a tumor in his lungs, you have to consider it malignant until proven to be benign.

[1] بالصدفة

Symptoms of lung cancer:

A) General (these are symptoms seen in patients of all types of cancers):

1. **Cachexia (weight loss)**: severe weight loss in a short period of time
2. **Iron deficiency anemia**
3. **Muscle wasting**: which will lead to weakness & fatigue

B) Organ specific symptoms (in this case; the lung)

1. **Pleural effusion**:

   This symptom in particular is a problem for doctors because many diseases also present with pleural effusion (ex: pneumonia, cirrhosis[2], congestive heart failure).

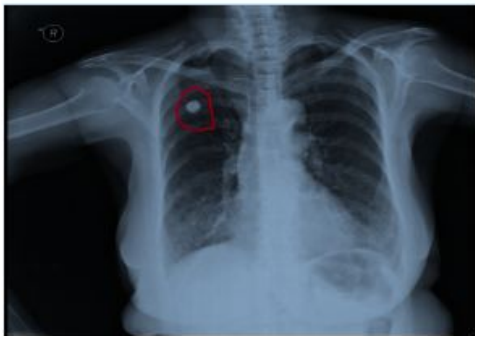
   The fluid can either be [exudate or transudate *(read footnote)*][3].
2. **Chest pain**
3. **Dyspnea**
4. **Hemoptysis**: coughing up blood
5. **Hoarseness**: abnormal voice changes (think of it as if a horse could talk)
6. **Atelectasis**: collapse or partial inflation of lung
7. **Pancoast tumor** (superior sulcus tumor):

   involvement of the apex of the long, often with **Horner syndrome** (ptosis, miosis and anhidrosis[4]) due to the involvement of the cervical sympathetic plexus.

Benign tumors:

The most common benign tumor of the lung is spherical, small, discrete *hamartoma*[5] that often show up as so called coin lesion in chest radiographs. It is sometimes referred to as "*leave me alone lesion*" because it is only sitting there.

X ray shows hamartoma coin lesion



[2] liver disease

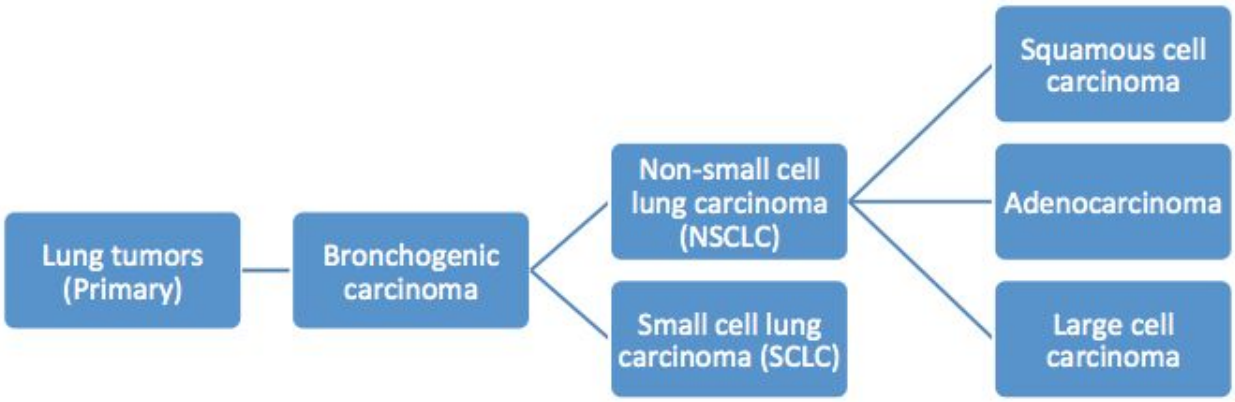
[3] *Exudate* fluid has a **high** protein content and is related to tumors while *transudate* has a **low** protein content and related usually to congestive heart failure.

[4] abnormal sweating (ex: loss of sweat in half of the face)

[5] an abnormal mass tissue in the organ, theses tissues are indigenous (محلي) to that site. In the lung it consists mainly of *mature cartilage*, but this sometimes admixed fat, fibrous tissue and blood vessels in various proportions.

Malignant tumors (primary):

We won't be talking about secondary tumors of the lung because mostly every malignant cancer can metastasize to the lung and will thus be discussed in later blocks.



Common etiopathogenic factors for all bronchogenic carcinomas:

A. **Air pollution**.
B. **Radiation:** incidence increased in radium/uranium workers.
C. **Asbestos:**
   increased incidence with asbestos and greater increase with combination of asbestos and cigarette smoking.
D. **Industrial exposure to nickel and chromate.**

Etiology and epidemiology:

- Bronchogenic carcinoma is the leading cause to death from cancer in both men and women. It is increasing in incidence, especially in women, in parallel with cigarette smoking.
- This type of carcinoma is directly proportional in incidence to the number of cigarettes smoked daily and to the number of years of smoking. Various histologic changes, including squamous metaplasia of the respiratory epithelium often with atypical changes ranging from dysplasia to carcinoma in situ precede bronchogenic carcinoma in cigarette smokers.
- Women have a higher susceptibility to carcinogens in tobacco than men. (Reason is unknown)

Clinical manifestations:

Carcinomas of the lung are silent, insidious lesions that in many cases have spread so as to be unresectable before they produce symptoms. In some instances, chronic cough and expectoration call attention to still localized, resectable disease. May include cough, hemoptysis and bronchial obstruction, often with atelectasis and pneumonitis. Other clinical features include:

1. **Superior vena cava syndrome:**

   Compression or invasion of the superior vena cava, resulting in facial swelling and cyanosis along with dilation of the veins of the head, neck and upper extremities.

2. **Pancoast tumor (superior sulcus tumor):**

   involvement of the apex of the lung. Often with Horner syndrome (ptosis, miosis and anhidrosis): due to involvement of the cervical sympathetic plexus.

3. **Hoarseness from recurrent laryngeal nerve paralysis.**

4. **Pleural effusion:** often bloody (bloody pleural effusion suggests malignancy, tuberculosis or trauma).

5. **Paraneoplastic endocrine syndrome:**

   The most frequent of which is adrenocorticotropic hormone (ACTH) or ACTH-like activity with small cell carcinoma; also of note are the syndrome of inappropriate diuretic hormone secretion with small cell carcinoma of the lung and parathyroid-like activity with squamous cell carcinoma.

   It is variously estimated that 3% to 10% of all patients with lung cancer develop clinically overt paraneoplastic syndromes. (e.g., Cushing syndrome and clubbing of fingers)

Overall, NSCLCs carry a better prognosis than SCLCs.

By the time these symptoms make an appearance, the prognosis is grim.

1) Squamous cell carcinoma:

If you smoke; this lecture should be more than enough to make you quit.

- ➔ Arises from squamous cells. Tends to arise centrally in major bronchi and eventually spread to local hilar nodes. Large lesions may undergo central necrosis, giving rise to cavitation.
- ➔ It's the leading cause of death from cancer in both men and women and is closely related to **smoking**.
- ➔ It's a very dangerous cancer if not diagnosed early; the 5 year survival rate is less than 5% and the tumor will often spread by local extension into the *pleura, pericardium, or ribs.*

This type of carcinoma is **directly proportional** in incidence to the number of cigarettes smoked daily and to the number of years smoking.

Various histologic changes are seen including squamous metaplasia of the respiratory epithelium often with atypical changes ranging from dysplasia[6] to carcinoma in situ precede bronchogenic carcinoma in cigarette smokers.

Clinical presentation:

Because of the close correlation with smoking; one of the signs is completely smoking related.

a) **Tar-stained fingers.** b) **Clubbing.** c) **Chronic obstructive disease.** d) **Cor pulmonale[7].**

How will squamous cell carcinoma take its course?

Irritation of the respiratory epithelium by the chronic irritant (smoking)

- ➔ Ciliated respiratory epithelium undergoes squamous *metaplasia* (which ***might*** lead to a chronic obstructive airway disease)
- ➔ After that if he doesn't quit smoking metaplasia will turn into dysplasia
- ➔ Carcinoma in situ (when dysplastic changes involve the entire thickness of the epithelium)
- ➔ Squamous cell carcinoma.

We can perform a cytology test (**sputum specimen**) to know the extent of the disease.

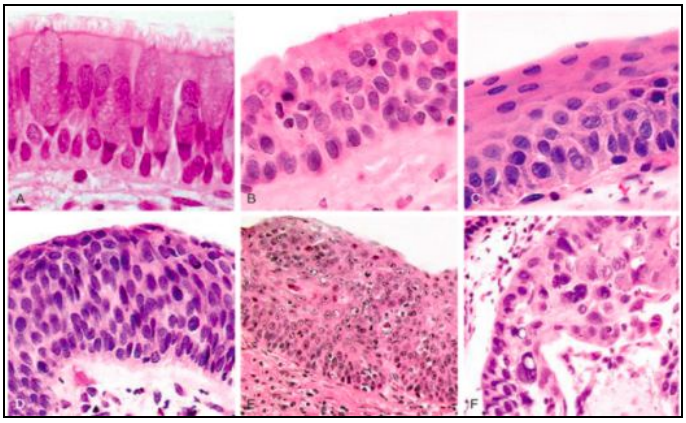
---

[6] Present with signs of malignancy however; there is no spread (it doesn't invade the basement membrane); so it's a premalignant cellular change where the cells becomes atypical.

[7] abnormal enlargement of the right side of the heart as a result of disease of the lungs or the pulmonary blood vessels

If we examine our specimen; we will notice the following neoplastic changes:

A. Nuclear hyperchromasia
B. Nuclear irregularity (abnormal cytoplasm ratio)
C. Nuclear pleomorphism[8]
D. Mitosis



Biopsy:

A well-differentiated[9] squamous cell carcinoma biopsy shows **keratin pearls** and **desmosomes**[10].

Gross presentation:

We will see a *big mass* that is mostly always **central** with a **black carbon pigment** (as a result of smoking and or air pollution). We may also note **obstruction of the bronchus** because of hilar lymph node involvement.

This large mass can *metastasize* to the **lymph node** and produce the characteristic **paraneoplastic syndrome**. Which is the presence of signs and symptoms indirectly related to cancer; for example *hypercalcemia* (a protein secreted which is similar to PTH increases CA levels) which is especially seen in squamous cell carcinoma.

2) Adenocarcinoma (scar carcinoma):

Unlike squamous cell carcinoma, adenocarcinoma is **not** associated with smoking and the tumor mass is **peripheral/subpleural** to the lung. Most common type of lung cancer in women and nonsmokers. Adenocarcinoma is **bronchial-derived** and develops on site of prior pulmonary inflammation or injury (usually on the periphery like mentioned). It's a *glandular* neoplasm that produce mucin secreting glands.

[8] variation in the size and shape between cells
[9] cancer cells look and behave like the normal cells in the tissue they started to grow in. They tend to be slow growing and less aggressive.
[10] Areas that help squamous cells adhere to each other; or in other words are intercellular bridges that link the cells together

It recently got changed to 2 classifications:

1) Adenocarcinoma in situ[11]:

Often involves peripheral parts of the lung, as a single nodule. The key features of AIS are diameter of 3 cm or less, growth along pre-existing structures, and preservation of alveolar architecture

2) Invasive adenocarcinoma.

EGFR gene & treatment:

25% of patients have the mutated **EGFR** (epithelial growth factor receptor) gene which produces this carcinoma; if a patient tests positive for this gene we can use **anti EGFR** (by targeted therapy) for treatment & therapy.

Anti EGFR can also be coupled with excision of the mass if needed..

Neuroendocrine carcinoma:

Grade	Refers to what degree a cell histologically relates to its mother cell (differentiation).
Stage	Refers to the clinical assessment. T: Size of mass. N: Number of lymph nodes involvement. T: Metastasis.

3) Carcinoid (well-differentiated):

Malignant tumors composed of cells that contain dense-core neurosecretory granules in their cytoplasm and, rarely, may secrete hormonally active polypeptides.

They are classified into typical (low-grade) and atypical (intermediate-grade) carcinoids; both are often resectable and curable.

Most carcinoid tumors manifest with signs and symptoms related to their intraluminal growth (i.e., they cause cough, hemoptysis, and recurrent bronchial and pulmonary infections).

Peripheral tumors are often asymptomatic, being discovered incidentally on chest radiographs.

Mass usually **central (can be peripheral),** secretes vasoactive amines such as **serotonin** that can cause carcinoid syndrome (rarely) leaving the patients with symptoms like diarrhea, bronchospasm, thrashing, cyanosis, etc.

[11] Characterized by severe dysplasia; however still confined.

4) Neuroendocrine carcinoma (moderately-differentiated): The mass is usually **peripheral**.

5) Neuroendocrine carcinoma [Small cell/Oat [12]cell carcinoma] (no differentiation)

Generally appear as pale gray, centrally located masses with extension into the lung parenchyma and early involvement of the hilar and mediastinal nodes. Necrosis is invariably present and may be extensive.

It's an aggressive cancer with a bad prognosis, it kills patients within 6 to 12 months; this is because by time of diagnosis the tumor has already metastasized. Like squamous cell carcinoma, this is also related to **smoking** and is more commonly seen in **men**. It presents as a hilar/perihilar mass.

- It's responsible for ectopic production **ACTH** (adrenocorticotropic hormone) which stimulates adrenal cortisol release.
  [High cortisol levels → **cushing's syndrome** (moon-face, redness in cheeks, females will develop facial hair).]
  As well as **ADH** (anti-diuretic hormone) which controls urine secretions.

- **Treatment:** We cannot excise it and must use chemotherapy.

6) Anaplastic carcinoma (large cell carcinoma):

Anaplastic carcinoma usually has a low degree of differentiation; it can show features of squamous cell or adenocarcinoma on electron microscopy.

If diagnosed early, mass can be excised else we need to depend on chemotherapy.

Diseases of the Pleura:

Can be divided for practical purposes into:

A. **Inflammatory conditions (pleuritis):** Which can be acute or chronic and is often caused by pyogenic organisms or tuberculosis causing empyema, pleural effusion and adhesions.

B. **Neoplastic lesions of the pleura:** Which can be caused by direct spread of a bronchogenic carcinoma, metastases from other parts of the body (secondaries) or a primary neoplasm called **mesothelioma.**

Diagnosis of the pleura diseases in general is made by:

- Radiological investigations.
- Bacteriological assessment and culture.
- Cytological and histological assessments (cytological examination of pleural fluid and also pleural biopsies)

[12] It's called oat because the nuclei look like oat (حبة الشعير)

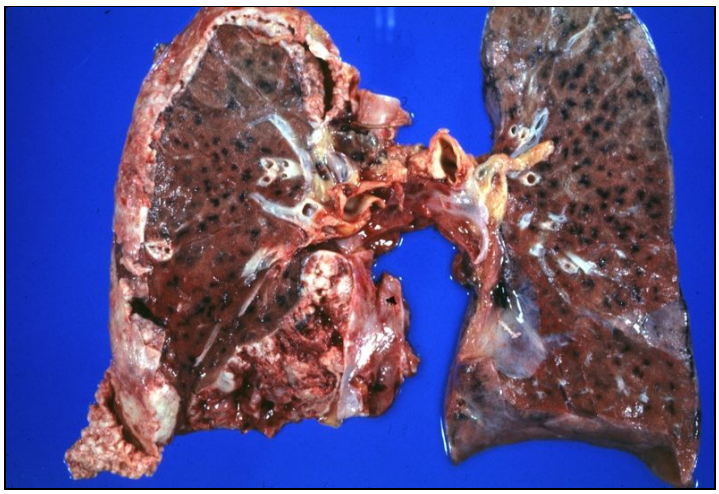
Mesothelioma:

Malignant transformation of mesothelial cells (found in pericardium/pleura) of lung, it unfortunately has a bad prognosis and those affected by it usually die.

- ➔ Rare except after exposure to asbestos.
- ➔ After exposure, there may be a latent period of up to 50 years before development of the tumor.
- ➔ Exposure to asbestos also causes development of benign collagenous thickening of the pleura termed pleural plaques.
- ➔ Patients usually present with chest pain and breathlessness and there is commonly a pleural effusion.
- ➔ Mesotheliomas are highly malignant tumors that spread to adjacent structures like the pericardium and lung and death usually occur 10 months after diagnosis, although metastases are rare.

Gross image of mesothelioma

In the gross image we can see that it encases and compresses the lung.



- ➔ Preceded by extensive pleural fibrosis and plaque formation, These tumors begin in a localized area and over time spread widely, either by contiguous growth or by diffusely seeding the pleural surfaces.
- ➔ Asbestos is not removed or metabolized from the lung, so the fibers remain in the body for life. Thus, the lifetime risk after exposure does not diminish over time (unlike with smoking, in which the risk decreases after cessation).

Contact us: pathology435@gmail.com

Team members

Nouf Altwaijri

Aljohara Almazroua

Ghaida Aljamili

Kowthar Almousa

Nojood Alhaidri

Nouf Alabdulkarim

Raghad Alnafisah

Rawan Aldhuwayhi

Reem AlAgeel

Samar AlOtaibi

Wael Al Oud

Abdulaziz AlHammad

Abdullah AlGhizzi

Abdulrahman Thekry

Ahmad Alkhiary

Ammar Almansour

Anas Ali

Faris Alwarhi

Khalid Ali Alghsoon

Mana AlMuhaideb

Naif Alhadi

Saleh Alkhalifa

Rayan Almuneef

Salem Al Ammari

قال صلى الله عليه وسلم: من سلك طريقاً يلتمس به علماً سهل الله له به طريقاً إلى الجنة.

دعواتنا لكم بالتوفيق.