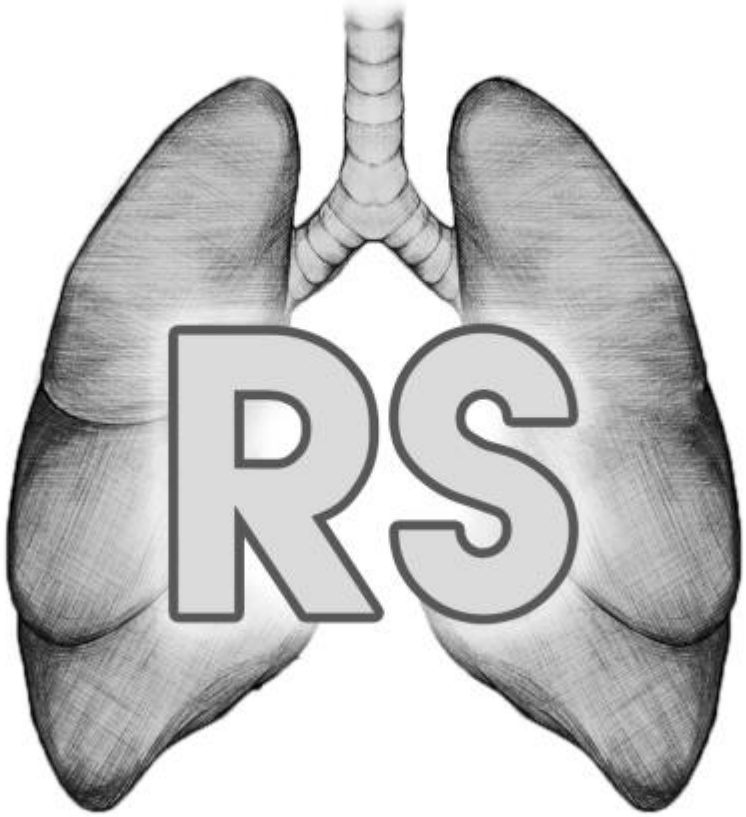

Sheet ○Slide ○Handout

Number

8

Subject

TB & Lung Cancers

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Correction team

Doctor

Dr. Heyam Awad

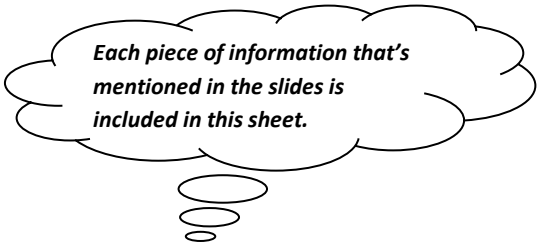
Date: 00/00/2016

Price:

By The name of Allah The Compassionate The Merciful

Topics of the lecture :

1. **Tuberculosis " TB "**
2. **Lung Cancers .**



Tuberculosis "السّل"

- Tuberculosis is a **communicable** ***Granulomatous*** **chronic disease**
- **Epidemiology**
  - It flourishes under conditions of poverty, crowding, in old people and disease states such as
    a) Diabetes mellitus
    b) Hodgkin lymphoma
    c) Silicosis
    d) Immunosuppression.. Including AIDS.
  - *Is TB Common ?!*
    in some areas ; Africa and Southeast Asia " Poor areas " and in the western countries there is increase in the incidence of TB because of its association with HIV although they worked hard to good control of the TB through the vaccination and better living conditions !
  - *Infecting with TB now is more dangerous than before 30-40 years ago ; because of the resistance!*
  - only a small fraction *" 10% "* of those who contract an infection develop active disease *; then we have to differentiate between disease and infection !!*

- **Etiology**: mycobacterium tuberculosis which are acid fast bacilli " *Tubercle bacilli " what makes them dangerous is their ability to prevent the macrophages from phagocyte them !*

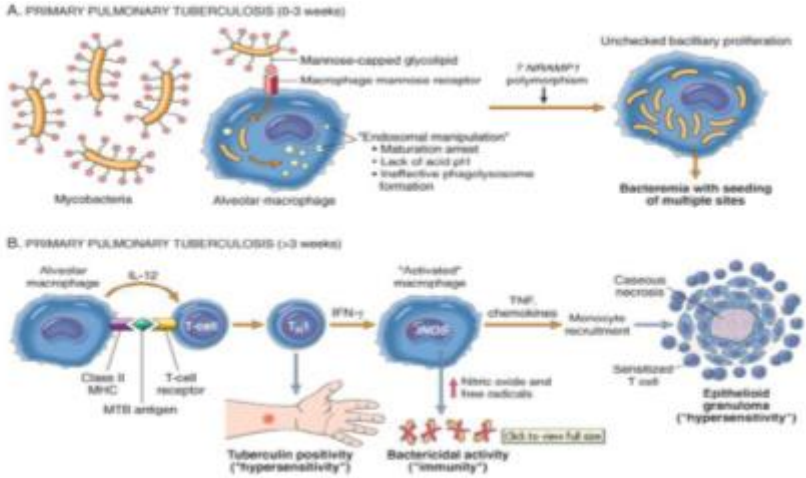
- **Pathogenesis : "** *similar to the pathogenesis of other granulomatous diseases but here the etiology is known ! "*
  I. **In** the **first 3 weeks** of infection:
     - ✓ Once the mycobacteria gains entry into the macrophage endosomes , the organisms are able to ***inhibit normal microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole*** and this allows *unchecked mycobacterial proliferation.*
     - ✓ It is characterized **by bacillary proliferation** within the alveolar macrophages with resulting **bacteremia**
     - ✓ ***Asymptomatic or flu-like illness !***

  II. **3 weeks after** exposure :
     Development of **cell-mediated immunity**
     - ✓ Processed **mycobacterial antigens reach the draining lymph nodes** and are presented to CD4 T cells **by macrophages which secret IL-12**, which stimulates **TH1 subtype of CD4+ T** cells that secret **Gamma- IFN** which activates **macrophage ,** accumulation of the macrophages result in **Granulomas !**

- ✓ Activated macrophages release a variety of mediators
    1) TNF, which is responsible for recruitment of monocytes, which in turn undergo activation and differentiation into the "epithelioid histiocytes
    2) Expression of the inducible nitric oxide synthase (iNOS) gene, which results in elevated nitric oxide levels with antibacterial activity;
    3) Generation of reactive oxygen species, which can have antibacterial activity.

❖ **Note:**

- ✓ It is important that infection be differentiated from disease.
- ✓ Infection implies seeding of a focus with organisms, which may or may not cause clinically significant tissue damage (i.e., disease).



❖ **Tuberculin test :**

- ✓ *Taking a purified protein from the bacilli and inject it under the skin of the patient* ***"*intracutaneous injection of 0.1 mL of PPD"** *and wait* ***2-3 days*** *to read the results because we are talking about* the development of **delayed hypersensitivity** .

- ✓ This injection induces **a visible and palpable induration** surrounded by erthyma " redness " , is that enough ?! No , we have to measure **the diameter of indurated area without the erthyma** >>> it should be at least 5 mm in diameter to say it's positive !
  >>> it should be 15 mm to be sure that it's really TB !

- ✓ Very important note : the test is done **about 2 to 4 weeks after the infection** has begun why?!
  hypersensitivity reaction needs around 3 weeks to stimulate the T helper cells because as we said in the pathogenesis the first 3 weeks it's all about the proliferation of the bacilli in the macrophages , after 3 weeks the cell- mediated immune reaction occurs .
- ✓ To sum up :
  we do the test after 3 weeks of exposure to the bacteria and wait 2-3 days to read the results!
- ✓ **Please if you are usure in your reading take a second opinion!!!!**

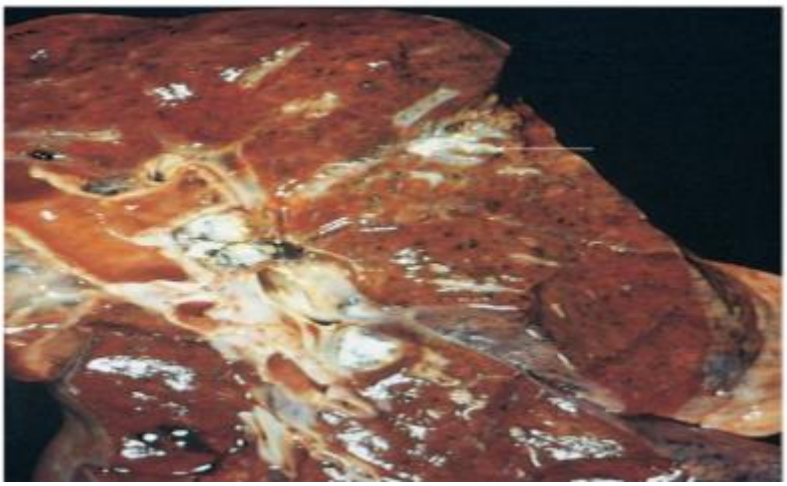
- ✓ *When would we use this test ?*
  *** close contact with infected patients :*
  - *Doctors treat patient with TB .*
  - *Patient come with flu like illness and one or more of his family members infected with TB .*

- ✓ A positive tuberculin skin test Signifies cell-mediated hypersensitivity to tubercular antigens but it doesn't differentiate infection from disease
- ✓ False-negative tuberculin reactions (or skin test anergy)
  occurs when the T helper cells are busy in killing something else not interested in the protein that we inject ! like in :
  a. Certain viral infections,
  b. Sarcoidosis
  c. Immunosuppression (low level of T helper cells then in some cases the HIV gives false negative result)
  d. Overwhelming Sever TB infection **How Come ?!** the T helpers are working in lungs to kill the bacilli there then no enough T helper to react with this injected protein .

- ✓ False-positive reactions may result from infection by **atypical mycobacteria** because it's similar to TB bacilli .
- ✓ About 80% of the population in certain Asian and African countries is tuberculin positive.
- ✓ About 3% to 4% of previously unexposed persons acquire active tuberculosis during the first year after "tuberculin conversion," and no more than 15% do so thereafter.

❖ **Primary TB**:

- ✓ Is the form of disease that develops in previously unexposed and unsensitized patient.
  " **it is the first time the patient expose to the Bacilli "**
- ✓ The inhaled bacilli implant in the alveoli of the **of the lower part of the upper lobe or the upper part of the lower lobe, usually close to the pleura.**
- ✓ 2-3 weeks after exposure , a 1-to 1.5- cm lesion develops (Ghon focus) composed **of caseating "cheese like " granulomas**
- ✓ **Caseating** Granulomas in the primary lung site : **Ghon focus**
- ✓ **Ghon focus** and granulomas in draining **lymph nodes** = Ghon **complexes**.
- ✓ The **Ghon complex undergoes** progressive fibrosis, followed by



radiologically detectable **calcification** (**Ranke complex**).

- ✓ It's very important in clinical to know each of the Ghon Focus " the first focus of the disease which is **caseating granulomas** " , Ghon complex " Ghon focus + lymph node involvement " , Ranke Complex " calcified Ghon complex "

- ✓ **The major consequences of primary tuberculosis are that**
  1) It induces hypersensitivity and increased resistance;
  2) The foci of scarring may harbor viable bacilli for years, perhaps for life, and thus be the nidus for reactivation at a later time when host defenses are compromised. { become dormant and activated into secondary TB}
  3) uncommonly, it may lead to direct progressive primary tuberculosis into the secondary without the dormant stage and this complication occurs in patients who are immunocompromised .

❖ **Secondary TB**:

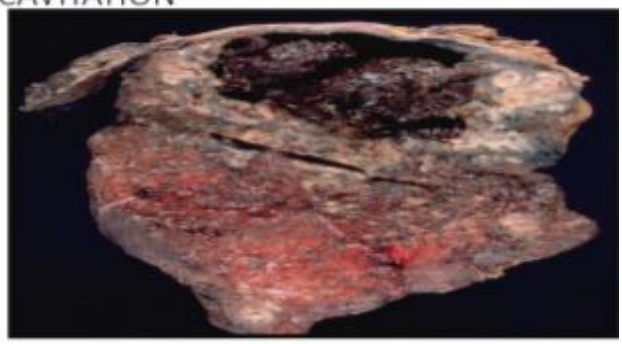
- ✓ Is the pattern of disease that arises in a previously sensitized host.
- ✓ The secondary TB may :
  A. It may follow **shortly after primary tuberculosis** in immunocompromised
  B. More commonly arises from **reactivation of dormant primary TB** decades after initial infection, particularly when host resistance is weakened.
  C. It also may result from **exogenous reinfection** because of waning of the protection afforded by the primary disease.
- ✓ Only a few patients with primary disease subsequently (5%) develop secondary tuberculosis.

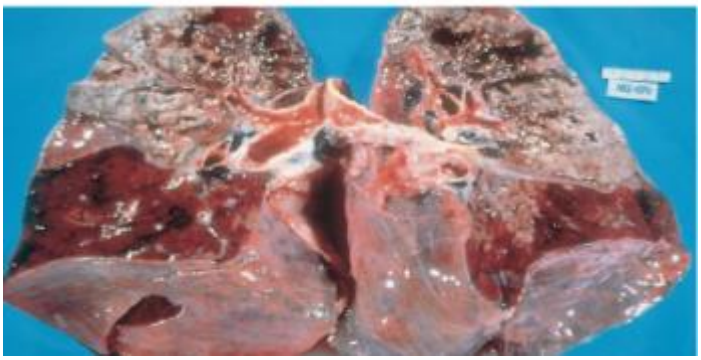
- ✓ Secondary tuberculosis is classically **localized to the apices of upper lobes related to high oxygen tension in the apices because it's aerobic bacteria .**
- ✓ As a result of this localization, *the regional lymph nodes are less prominently involved early in the disease than they are in primary tuberculosis.*
- ✓
- ✓ **Cavitation** occurs in the secondary form, leading **to erosion into and dissemination** along airways. **Why not seen in the primary ?!** Because of the preexistence of **hypersensitivity,** the bacilli excite marked tissue response to wall off the focus { more tissue destruction }

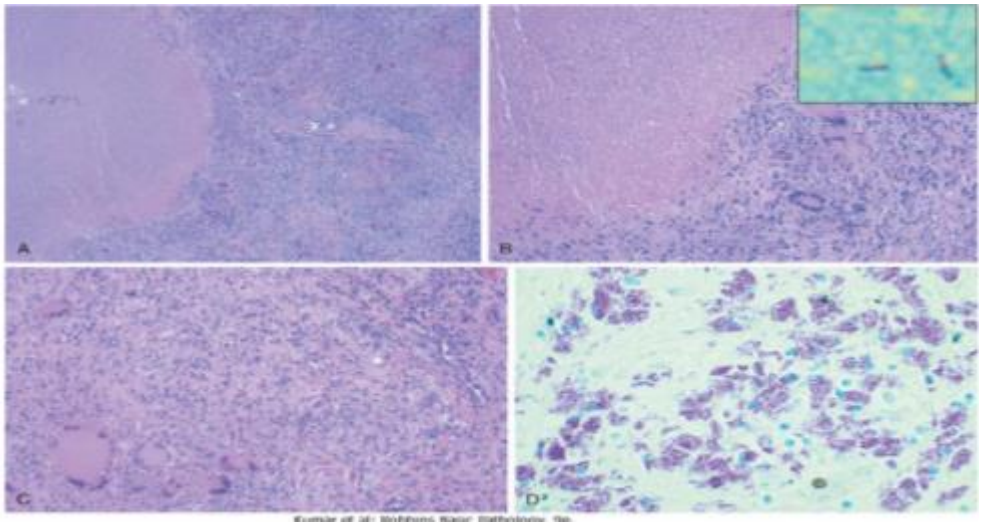
- ✓ **Morphology of secondary TB**

  - The initial lesion usually is a small focus less than 2 cm within 2 cm of the apical pleura.
  - Erosion of blood vessels results in hemoptysis
  - With adequate treatment, the process may be arrested, although healing distorts the pulmonary architecture

CAVITATION

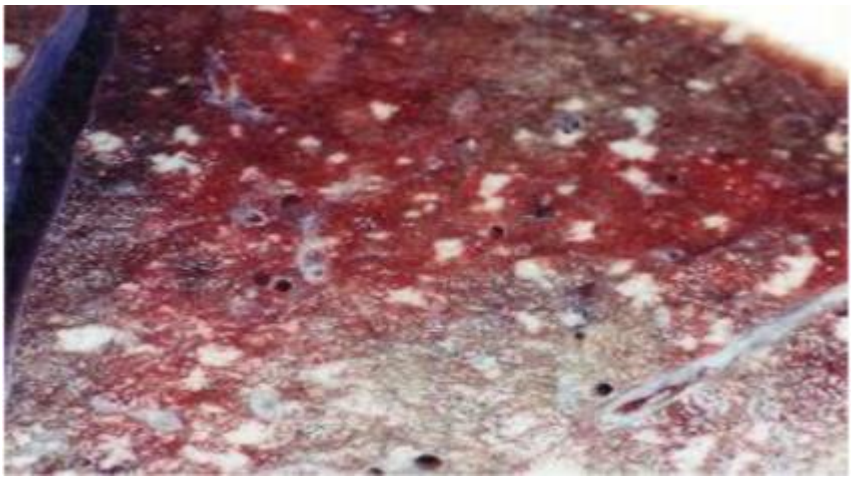






NOTE : if we see a similar morphology in the lower lobes >>> think of cancer .

- **Miliary pulmonary disease**
  - **Miliary from Millet** " الذرة البيضاء " **,** means that showers from the bacteria go out from the lung through the lymphatics or the blood vessels .
  - Occurs when organisms drain through lymphatics into the lymphatic ducts, then empty into the venous return to the heart and then into the pulmonary arteries return back to the lungs .
  - Individual lesions are small, (2 mm) foci scattered through the lung parenchyma Pulmonary .



❖ **Systemic miliary tuberculosis**

- Occurs when the organisms disseminate **through the systemic arterial syste**m to almost *every organ in the body and is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis*

❖ **Isolated-organ tuberculosis**

- Tuberculous involvement of Vertebrae is called (Pott disease) .
- it can also affect the fallopian tube and result in infertility .

❖ **Clinical Features**

- ✓ The primary focus is it always in the lungs ?! yes , can see also in the GI " bovine bacilli"
- ✓ The bovine bacilli now is decreased why ?! because of milk pasturalization .
- ✓ Localized secondary tuberculosis may be asymptomatic
- ✓ If symptomatic, symptoms are insidious in onset.
- ✓ Systemic manifestations, include malaise, anorexia, weight loss, low grade fever, and night sweat
- ✓ With progressive pulmonary involvement, increasing amounts mucopurulent sputum
- ✓ Some degree of hemoptysis is present some cases of pulmonary tuberculosis.
- ✓ pleuritic pain
- ✓ Extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved for example,:
    a. Tuberculous salpingitis may present as infertility.
    b. Tuberculous meningitis with headache and neurologic deficits.
    c. Pott disease with back pain and paraplegia.

Lung Carinoma

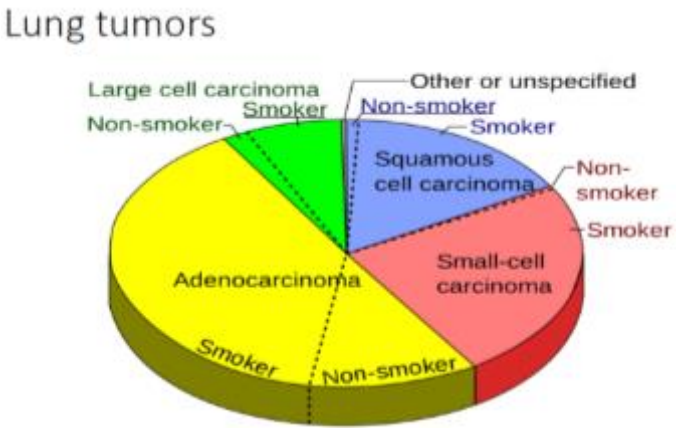
❖ Lung tumors are killers and really common ☹!.

❖ The most common cancer among the males >> prostate cancer, among females >> Breast cancer. In general , the lung cancer is the killer #1 .

❖ Lung tumors : carcinoma , lymphoma and sarcoma .

❖ **primary** lung cancer is a common disease accounting for 95% of primary lung tumors

❖ Carcinoma: Is the single most important cause of cancer-related deaths in industrialized countries accounts for **about one third of cancer deaths in men, and has**



become the leading cause of cancer deaths in women.

- The peak incidence of lung **cancer is in persons in their 50s and 60s.**
- The prognosis with lung cancer is dismal:
  1. The 5- year survival rate for all stages of lung cancer combined is about 16%.
  2. Disease **localized** to the lung, the 5-year survival rate is **45% .**

- The four major **histologic types** of carcinomas of the lung " the most common "
  a. Adenocarcinoma
  b. Squamouscell carcinoma,
  c. Small cell carcinoma,
  d. Large cell carcinoma
  - All of these carcinomas are related to smoking ,but the **S**mall cell carcinomas and **S**quamouscell carcinoma are related to **S**moking more than others. { strongest association }
  - In **Adenocarcinoma** ok the smokers are more than the nonsmoker , but percentage of the them **nonsmokers** is really large ! >>> then if a patient with lung cancer who is **non smokers** ,usually **young**, most probably the type of carcinoma is Adenocarcinoma . also, it's the most common lung cancers **in women** .

- Because **of changes in smoking patterns** in the U.S., **adenocarcinoma has replaced squamous cell carcinoma** as the most common primary lung tumor in recent years.

- Carcinomas of the lung were classified into two groups:
  a. Small cell lung cancer (SCLC) and
  b. Non-small cell lung cancer (NSCLC), including adenocarcinomas and squamous cell carcinomas.

- The reason for this historical distinction was that virtually all SCLCs have metastasized by the time of diagnosis and are not curable by surgery and are treated by chemotherapy, with or without radiation therapy.
- By contrast, NSCLCs were more likely to be resectable and usually responded poorly to chemotherapy however, now therapies are available that target specific mutated gene products present in the various subtypes of NSCLC, mainly in adenocarcinomas.

- **NSCLC must be classified into histologic and molecular subtype.**

- There is strong evidence that cigarette smoking and, to a much lesser extent, other environmental insults are responsible for the genetic changes in lung cancers.

- **About 90% of lung cancers** occur in **active smokers or those who stopped recently.**

- The increased risk becomes **60 times greater** among habitual heavy smokers (two packs a day for 20 years) than among nonsmokers.

- Since only 11% of heavy smokers develop lung cancer, however, other predisposing factors must play a role.

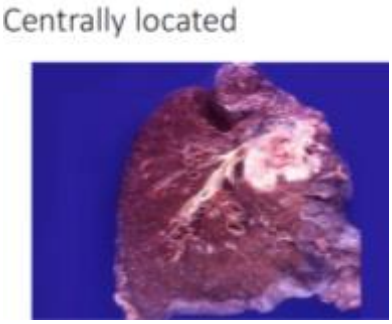
- The *mutagenic effect of carcinogens is conditioned by (genetic) factors.*
  - Many chemicals **(procarcinogens) require metabolic activation via the P- 450** monooxygenase enzyme system for conversion into ultimate **carcinogens**
  - Persons with **specific genetic polymorphisms involving the P-450 genes** have an **increased capacity to metabolize procarcinogen**s derived from cigarette smoke, and thus have the **greatest risk for development of lung cancer** , others may have decrease the capacity of the P-450 ; **this polymorphism explains why not all smokers develop lung cancer .**

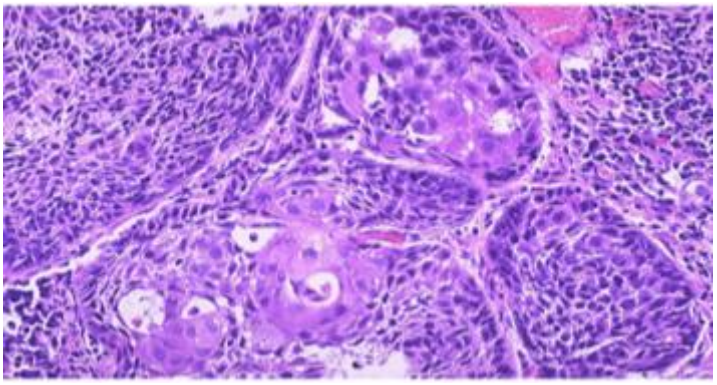
- For reasons not clear**, women have a higher susceptibility to carcinogens in tobacco than men.**
- **Although cessation of smoking decreases** the **risk** of developing lung cancer over time, **it may never return to baseline levels** depends on the accumulated mutation because the carcinogenesis is multi step process
- ***Passive smoking*** *increases the risk of developing lung cancer to* ***approximately twice that of nonsmoker.***
- The smoking of pipes and cigars also increases the risk, but only modestly
- There is increased incidence of lung carcinoma in asbestos workers; and workers exposed to dusts containing arsenic, chromium, uranium.
- Note
  - Exposure to asbestos increases the risk of lung cancer fivefold in nonsmokers.
  - 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

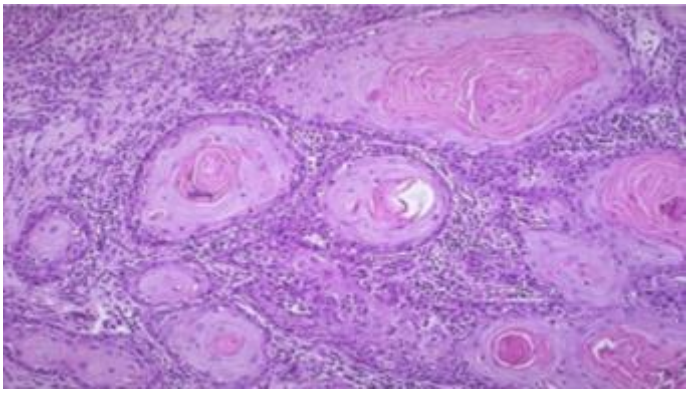
- Smoking-related carcinomas of the lung arise by a **stepwise accumulation of a multitude of genetic abnormalities** that result in transformation of benign progenitor cells in the lung into neoplastic cells
- The sequence of **molecular changes is not random** but follows a predictable sequence that parallels the histologic progression toward cancer.
  - **Inactivation of 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 are late .**
- **In Adenocarcinomas**
  A. Activating mutations of the **epidermal growth factor receptor (EGFR)** and these tumors are sensitive to agents that inhibit EGFR signaling, but the response often is short lived.
  B. **MET tyrosine kinase** gene amplifications
  C. In **4**% of adenocarcinomas **are EML4-ALK tyrosine** kinase .
- **ALK tyrosine kinase usually cause Large cell tumors with bad prognosis** although **These abnormalities are rare but they** are **important** because of their **therapeutic implications**, as they can be targeted with tyrosine **kinase inhibitors.**
-
- The identification of genetic alterations producing overactive EGFR, ALK, and MET has opened up a new era of "personalized" lung cancer therapy

❖ MORPHOLOGY

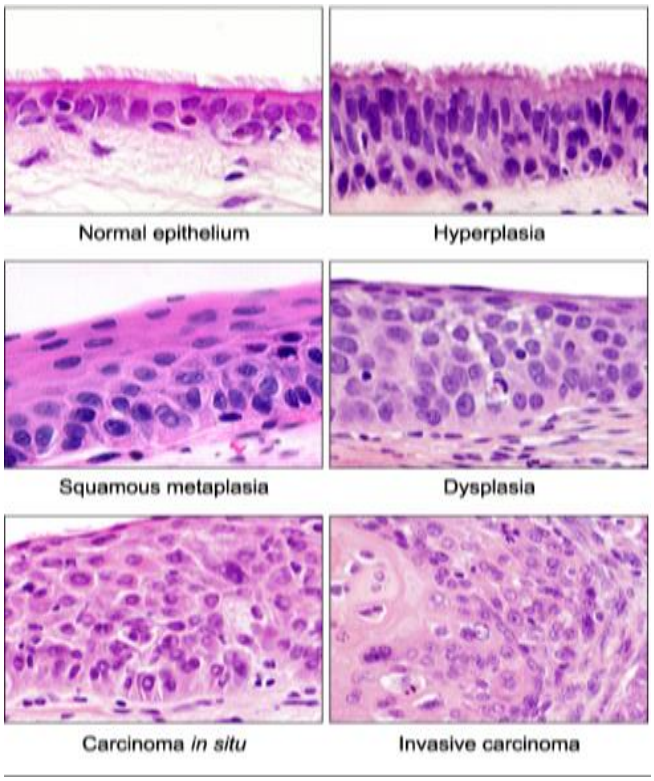
- **Squamous cell carcinomas :**
  I. Are more common in **men than in women**
  II. Are closely correlated with **a smoking history**;
  III. They tend to **arise centrally** close to major bronchi and eventually spread to local hilar nodes
  IV. Disseminate outside the thorax later than do other histological types
  V. Under the microscope , they produce **nest "group " of cells and they secret keratin** then it's squamous in origin . " individual cell keratinization "



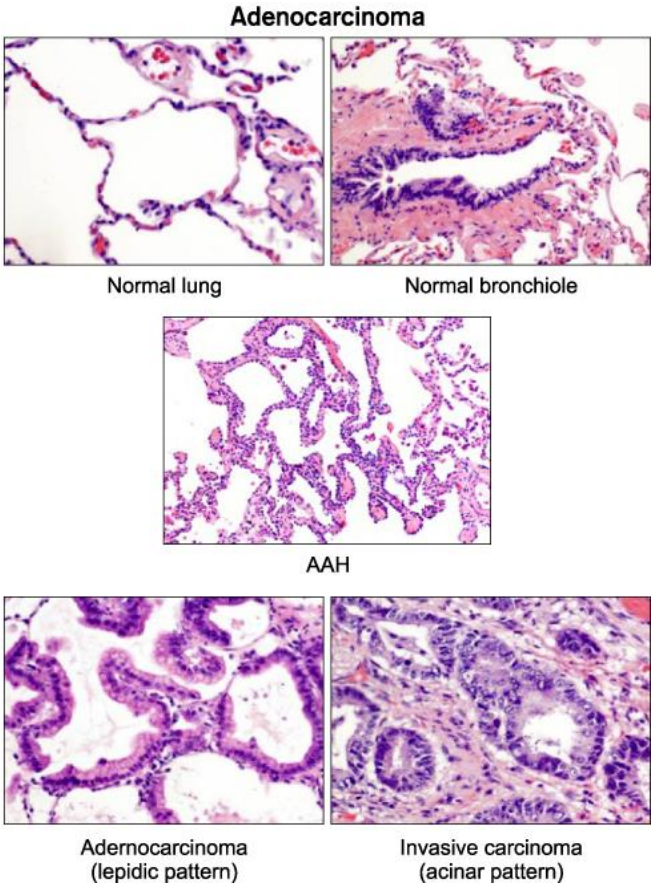




- The smoking is not directly cause carcinoma it's a multistep process ; at the beginning , normal epithelium "Psuedostratified ciliated columnar " , the smoking will trigger the hyperplasia of the cells then squamous metaplasia .then accumulation of the mutation that ends up with dysplasia by steps the carcinomas in situ develop then invasive squamous cell carcinoma .

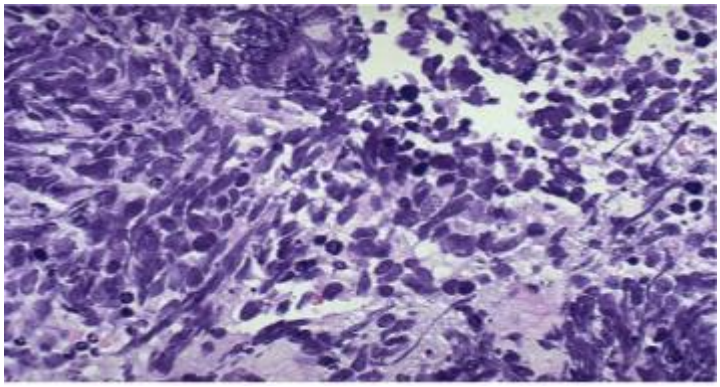


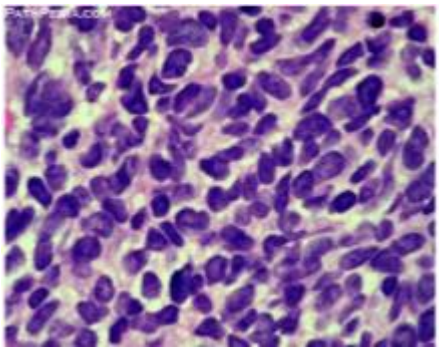
- **Adenocarcinomas:**
  I. May occur as central lesions but usually are **more peripherally located**, many with a central scar.
  II. Are the most common type of lung cancer in **women and nonsmokers.**
  III. **i**n general, adenocarcinomas grow slowly and form **smaller masses** than do the other subtype.
  IV. They tend to **metastasize** widely **at an early stage** ***{ faster than the squamous cell carcinoma* }**
  V. The sequence of the **Adenocarcinomas ;** the precursor of peripheral adenocarcinomas is **atypical adenomatous hyperplasia** which progresses to
     a. Adenocarcinoma in situ
     b. Minimally invasive adenocarcinoma (tumor less than 3 cm and invasive component measuring 5 mm or less),
     c. Invasive adenocarcinoma (tumor of any size that has invaded to depths greater than 5 mm).



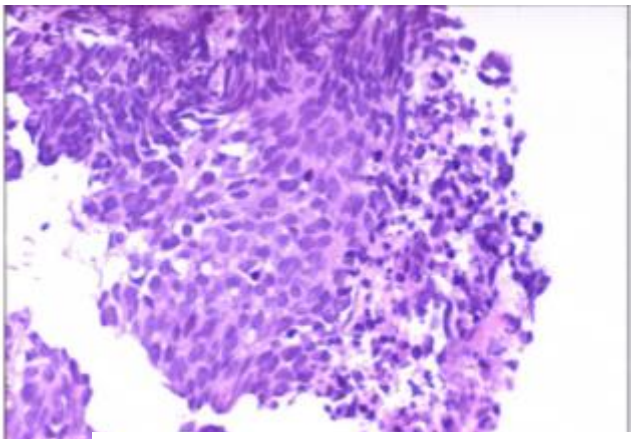
- **Small cell lung carcinomas (SCLCs) are:**
  I. **Centrally** located with extension into the lung parenchyma
  II. **Smaller than the adeno and squamous carcinoma but thet are larger than normal cells { 3 -4 times larger than the lymphocytes } . " small compared to the malignant not to the normal "**
  III. **Related to smoking .**
  IV. Early involvement of the hilar and mediastinal nodes.

V. Are composed of tumor cells with a round shape, scant cytoplasm, and finely granular chromatin with many mitotic figures .{ they are neither nest nor glands } . they grow independent { individual cell pattern } on each others which means that they lost the attachment { E-cadherin } >> they are neuroendocrine cell .





- Necrosis is invariably present and may be extensive
- Fragile cells that show fragmentation and "crush artifact".{ Characteristic for small cell carcinomas }
- Nuclear molding resulting from close apposition of tumor cells that have scant cytoplasm.


Crushing artefacts in small cell carcinoma

❖ Clinical Course

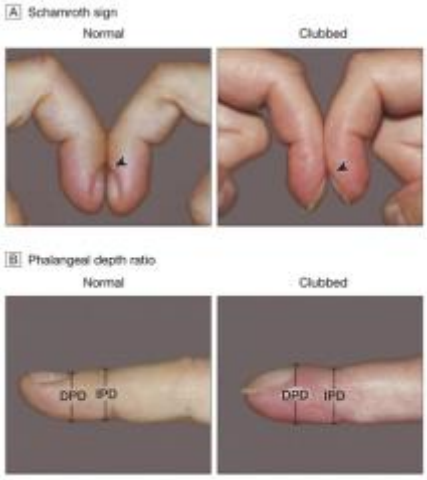
- Are silent, cancers that in many cases have spread so as to be unresectable before they produce symptoms.
- In some instances, chronic cough call attention to still localized, resectable disease.

- By the time hoarseness, chest pain, superior vena cava syndrome, pleural effusion, makes its appearance, the prognosis is grim

- Too often, the tumor presents with symptoms resulting from metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain).
- Although the adrenals may be nearly obliterated by metastatic disease, adrenal insufficiency (Addison disease) is uncommon,

- About 3% to 10% of all patients with all the types of lung cancer **especially the Small Cell Carcinomas.** develop clinically overt **parneoplastic syndromes {** certain symptoms in patient with cancer which cannot be explained by the local , metastasis or endogenous effect of the cancer **}** . these parneoplastic syndromes cause **:**

    1. Hypercalcemia: caused by secretion of a parathyroid hormone-related peptide by squamous cell carcinoma
    2. Cushing syndrome (production of Adrenocorticotropic hormone);by small cell carcinoma
    3. Syndrome of inappropriate secretion of antidiuretic hormone; by small cell carcinoma
    4. neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy and polymyositis
    5. clubbing of the fingers and hypertrophic pulmonary **osteoarthropathy** by any type of carcinoma " unknown reason but it could be another mutation in the growth factors mainly fibroblast growth factor "



Sorry for any mistake ^^
wish you all best of luck ☺