RESPIRATORY SYSTEM PATHOLOGY

Title: Sheet 7 – Lung Tumors Part 1

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In this lecture, and the upcoming lecture, we will be discussing *Lung Tumors.*

LUNG TUMORS

Lung cancer can be **primary** or **secondary**.

Secondary (metastatic tumors)

Are tumors that arise outside the lungs, and spread to the lungs through the blood stream, lymphatics or even directly.

- **The most common cancers that spread to the lungs are:**
  1. Breast
  2. Colorectal
  3. Renal
  4. Head and neck tumors
  5. Testicular
  6. Soft tissue sarcomas (like osteosarcoma and melanoma)

Primary Lung Tumors

Are tumors that develop/originate in the lungs.

- They can be benign or malignant.
- Roughly **95% of primary lung tumors** are carcinomas.

- The remaining 5% include:
  1. Carcinoids
  2. Mesenchymal tumors, like fibrosarcoma
  3. Lymphomas
  4. Few benign lesions

Hamartoma

- The name "*Hamartoma,*" which implies a developmental anomaly, is a *misnomer*.
- It is the most common benign tumor in the lung.
- **Clono-cytogenetic abnormalities** have been noted in this tumor; this makes it a benign neoplasm.

- **Gross Appearance:**
  - Spherical in shape
  - Small (1-4 cm)
  - Discrete

- **Chest Radiograph**
  - Coin lesion

- **Histologically/Microscopic appearance:**
  - Mature cartilage admixed with fat, fibrous tissue, and blood vessels.

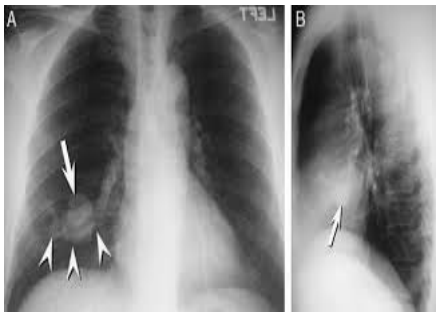


Figure 1: This radiographic image shows a coin lesion (Hamartoma)

Carcinoma of the Lung

As we've already mentioned, **95% of primary lung tumors are carcinomas**.

- It is the **most important cause of cancer-related deaths in industrialized countries**.
- This accounts for about 1/3 of cancer deaths in men.
- **The leading cause of cancer-related deaths in women.**

- **Incidence of Lung Carcinoma:**
  - Incidence among **males: Gradually decreasing**
  - Incidence among **females: Increasing**
    - Since 1987, the number of women dying of lung cancer each year is greater than the number of women dying of breast cancer.
    - This is related to the marked increase in the incidence of smoking in women over the past half-century.
  - The peak incidence of lung cancer is often in individuals who are in their 50's & 60's.

- **Upon diagnosis:**
  - More than 50% of patients **already have distant metastases.**
  - About ¼ of patients have **disease in the regional lymph nodes.**

- **Prognosis:**
  - Prognosis is dismal.
  - The 5-year survival rate for all stages of lung cancer combined is about 16%.
  - Prognosis has not changed over the last 35 years; even with the disease being localized to the lung. The 5-year survival rate is only 45%.

- **The Four Major Histological Types of Lung Carcinoma:**

1. **Adenocarcinoma**
2. **Squamous cell carcinoma**
3. **Small cell carcinoma**
   - A subtype of neuroendocrine carcinoma
4. **Large cell carcinoma**

- In some cases, there is a combination of histological patterns. For instance, you may find small cell carcinoma with adenocarcinoma.

*The table on the right shows the **2015 WHO classification of malignant epithelial lung tumors.***

- Out of the 4 major types of cancer, squamous cell and small cell carcinomas have the **strongest association with smoking**.
  (Adenocarcinoma is, to a lesser extent, associated with smoking).

Table 13.6 Histologic Classification of Malignant Epithelial Lung Tumors (2015 WHO Classification, Simplified Version)

Adenocarcinoma
Acinar, papillary, micropapillary, solid, lepidic predominant, mucinous subtypes
Squamous cell carcinoma
Large cell carcinoma
Neuroendocrine carcinoma
Small cell carcinoma
Large cell neuroendocrine carcinoma
Carcinoid tumor
Mixed carcinomas
Adenosquamous carcinoma
Combined small cell carcinoma
Other unusual morphologic variants
Sarcomatoid carcinoma
Spindle cell carcinoma
Giant cell carcinoma

- Adenocarcinoma:
  - Because of changes in smoking patterns in the US, adenocarcinomas have replaced squamous cell carcinomas as the **most common primary lung tumor in recent years**.

  - It is, by far, the **most common primary tumor** arising:
    1. In women.
    2. In people who have never smoked ('never-smokers').
    3. In individuals younger than 45 years of age.

- Lung carcinomas were previously classified into **two broad groups**:
  1. **Small cell lung cancer (SCLC)**
  2. **Non–small cell lung cancer (NSCLC)**
     - **NSCLCs** include:
       a. Adenocarcinoma
       b. Squamous cell carcinoma
       c. Large cell carcinoma
       d. Large cell neuroendocrine carcinomas

- This classification has been replaced with the more recent 2015 WHO classification (the table above [13.6]).

- The reason behind the old classification is the presence of shared features between tumors of the non-small cell lung carcinoma group (NSCLCs) , that are different from the shared features of the tumors of the small cell lung carcinoma group (SCLCs).
  - **The following table shows the different features:**

SCLC (Small Cell Lung Carcinoma)	NSCLC (Non-small cell lung carcinoma)
-Virtually, all cases will have **metastasized** by the time of diagnosis.	
- Not curable by surgery.	- More likely to be **resectable.**
- Best treated with systemic chemotherapy, with or without radiation therapy.	- Responds **poorly to conventional chemotherapy.** - **Targeted therapy** (therapy that targets specific onco-proteins) has evolved for treatment of **Adenocarcinoma and Squamous Cell Carcinoma.** - New immunotherapy approaches have been approved for the non-small cell carcinoma group and are being tested for the small cell carcinoma group.

- **Pathogenesis and Etiology of Lung Cancer:**

  - The development of lung carcinoma relies mainly on the **accumulation of genetic abnormalities after exposure to carcinogens**. This results in a **stepwise accumulation of driver mutations.**

  - These mutations transform the benign progenitor cells in the lung into neoplastic cells possessing all of the hallmarks of cancer.

  - So, the two crucial definite factors that lead to the development of lung carcinoma are:
    1. Exposure to strong carcinogens
    2. Accumulation of genetic abnormalities (due to exposure to carcinogens)

- **Predisposing genetic abnormalities:**

1. Inactivation of tumor suppressor genes located on **chromosome 3 (3p).**
   - An early event in lung cancer development

2. Mutations in **TP53** tumor suppressor gene and **KRAS oncogene.**
   - Occurs as a late event in lung cancer development

3. Mutations that activate the **epidermal growth factor receptor (EGFR).**
   - Stimulate *downstream pro-growth pathways*.
   - Is seen in a subset of adenocarcinomas, especially those that are associated with **non-smoker women.**

As we previously stated, the development of lung cancer is based on accumulation of genetic abnormalities after exposure to carcinogens. So, what are the main carcinogens that lead to this accumulation of mutations?

- **Main carcinogens:**

1. **Cigarette smoking**
   - The most important carcinogen.
   - There is strong evidence supporting the fact that cigarette smoking, and, to a lesser extent, environmental carcinogens are the main culprits responsible for development of mutations.

   - About **90% of lung cancers occur in active smokers or those who stopped recently.**
     - There is a linear correlation between the frequency of lung cancer and pack-years of cigarette smoking.

   - There is **increased risk of developing lung cancer** in:
     1) **Habitual heavy smokers**
        - The risk of lung cancer in habitual heavy smokers (those who smoke two packs a day for 20 years) is 60 times greater than in nonsmokers.
     2) **Women**
        - For unknown reasons, women are **more susceptible to carcinogens in tobacco smoke than men.**
     3) **Smoking of pipes**, cigars, and passive smoking (being in close proximity to a smoker).

- Although smoking cessation decreases the risk over time, it never returns to baseline levels.
  - **How come?** The resulting genetic changes can **persist** for many years in the bronchial epithelium of a former smoker.
  - Although **11% of heavy smokers** develop lung cancer, not all individuals exposed to tobacco smoke develop cancer.

- The development of lung cancer requires accumulation of genetic abnormalities after exposure to carcinogens, which result in a stepwise accumulation of mutations (refer to page 4).
- The mutagenic effect of carcinogens is modified by hereditary (genetic) factors.

2. **Environmental carcinogens**
   - Occupational exposures to some environmental carcinogens may sometimes be solely responsible for lung cancer, without the effect of smoking.
   - Examples:
     a. Uranium mines.
     b. **Work with asbestos.**
     c. Inhalation of dusts containing arsenic, chromium, nickel, or vinyl chloride.

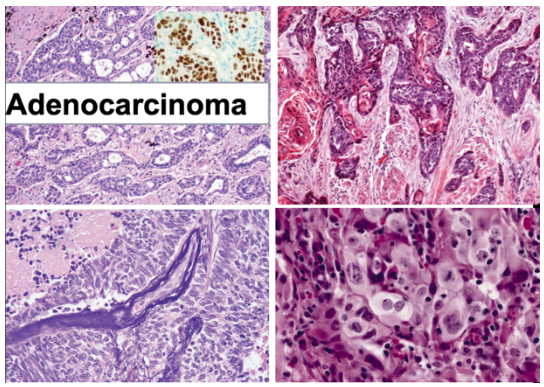
- **Asbestos and tobacco smoking**
  - There is a synergistic effect between asbestos and tobacco smoking.
  - Exposure to asbestos in **nonsmokers** increases the risk for developing lung cancer **5-fold.**
  - For **heavy smokers** who are exposed to asbestos, the risk is elevated approximately **55-fold.**

Like the adenoma-carcinoma sequence that is seen in colon cancer, for example, some invasive adenocarcinomas of the lung arise through a sequence, and start as:

Atypical adenomatous hyperplasia → adenocarcinoma in situ → Invasive adenocarcinoma sequence

Adenocarcinoma

This collage shows the histological representation of four types of lung cancer. **The image on the top left is that of adenocarcinoma**.

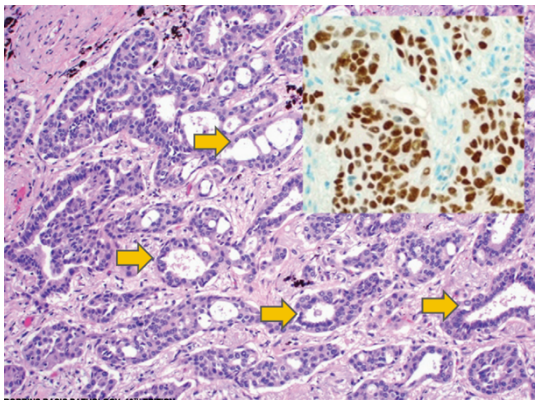


- **Location**: Usually peripherally located but may also occur closer to the hilum.
- **Growth**: Slowly growing tumors.
- **Size**: Form smaller masses, compared to other subtypes.
- **Metastasis**: Tend to metastasize widely at an early stage.

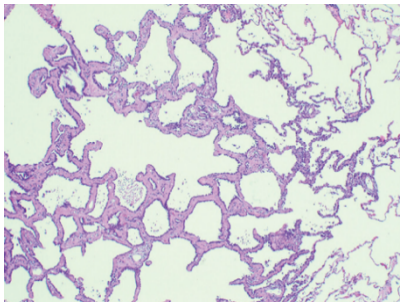
- **Morphology (microscopic)**

  - Variety of growth patterns, including:
    1. Acinar (gland-forming)
    2. Papillary
    3. Mucinous
    4. Solid types

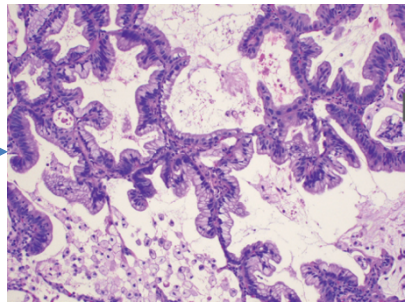
  - The microscopic image on the right shows many proliferating **gland-like structures (Acini)** surrounded by a dense desmoplastic reaction.
  - The small box on the top right corner shows **thyroid transcription factor 1 (TTF-1),** which is **positive**. The clue for positivity, is the brown nuclear staining.
  - We use **TTF1 immune stain** in histopathology lab to **highlight tumors of lung origin**. It shows **positive** expression in the majority of **pulmonary adenocarcinomas.**



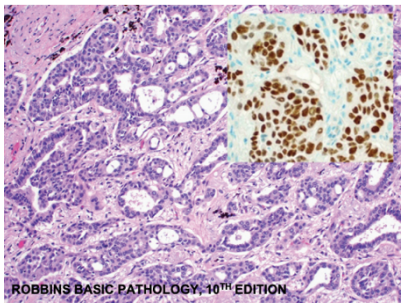
As we've already mentioned, pulmonary adenocarcinomas develop in a stepwise fashion, starting with a **precursor lesion** called **Atypical Adenomatous Hyperplasia (AAH)**. The AAH progresses to **adenocarcinoma in situ** in a stepwise fashion → progresses into **minimally invasive or invasive adenocarcinoma.**



Atypical Adenomatous Hyperplasia



Adenocarcinoma In situ



Minimally invasive or Invasive Adenocarcinoma

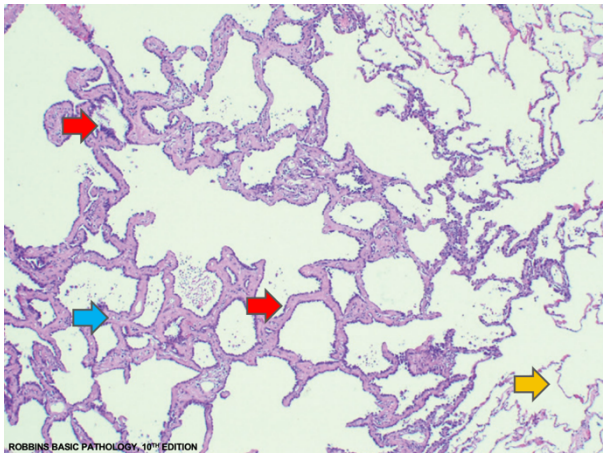
- **Atypical adenomatous hyperplasia:**

- Precursor lesion of adenocarcinoma.
- **Appearance**: well-demarcated focus of epithelial proliferation.
- **Diameter**: small lesion, ≤ 5mm.
- **Histologically:** (there is some degree of cytological atypia)
    - Composed of cuboidal to low-columnar cells.
    - Demonstrates nuclear hyperchromasia.
    - Pleomorphism.
    - Prominent nucleoli.

- Genetic analysis has shown that these lesions are monoclonal and share many molecular aberrations with adenocarcinomas (e.g., KRAS mutations).

This following figure shows features of atypical adenomatous hyperplasia.

- Red Arrow: Proliferation of hyperchromatic (blue/purple) cuboidal epithelial lining, which lines the alveolar walls.
- Yellow Arrow: (Right side) shows almost normal alveolar walls.
- Blue Arrow: Mild underlying interstitial fibrosis.



- **Adenocarcinoma in situ (AIS):**
- Formerly called **bronchioloalveolar carcinoma.**
- **Location**: Often involves peripheral parts of the lung as a single nodule.

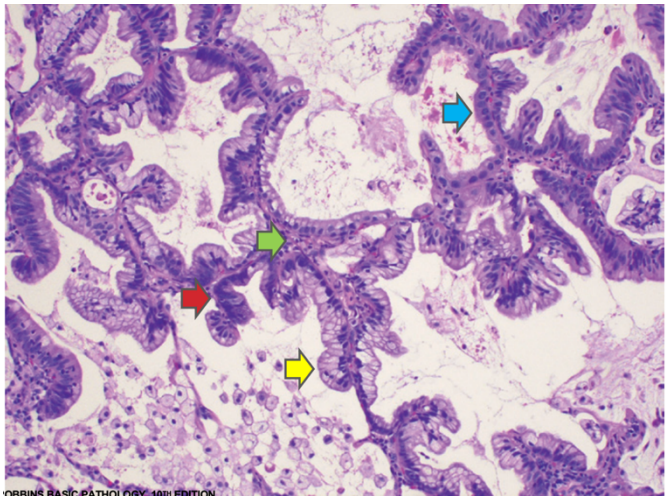
Key features for diagnosing AIS:

- diameter of ≤ 3 cm.
- Growth along preexisting structures (**no destruction of underlying structures**).
- Preservation of alveolar architecture.
- No destruction of alveolar architecture, or stromal invasion with desmoplasia (which is what is seen in Invasive Adenocarcinoma).
    - Destruction of the underlying structures, or the presence of desmoplastic reactions would mean/indicate invasion and infiltration.
- AIS is a **non-infiltrative tumor**.

- The tumor cells:
    - May be non-mucinous, mucinous, or mixed.
    - They grow in a monolayer along the alveolar septa, which serve as a scaffold for proliferation.

Note: Again, by definition, AIS does not demonstrate destruction of the alveolar structures or stromal invasion with desmoplasia. **If desmoplastic invasion and alveolar destruction is seen**, then this is a diagnostic feature of **Invasive Adenocarcinoma.**

This figure shows the mucinous subtype of AIS (Adenocarcinoma In Situ)



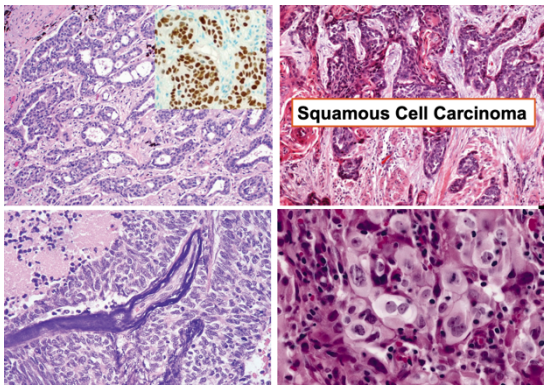
- Blue arrow: Monolayered proliferation of atypical cells. These atypical cells are proliferating along the **preexisting alveolar septa** (again, AIS grows along preexisting structures).
- **No destruction of the alveolar septa.**
- **No desmoplasia.**
- **No invasion .**

(All of the mentioned features prove this isn't Invasive Adenocarcinoma)

- Green arrow: Preexisting alveolar septa.
- Red arrow: Shows atypical proliferation, with a certain degree of **nuclear enlargement and hyper-chromasia** in these proliferating cells.
- Yellow Arrow: Apical Mucin (which explains why this demonstrates the mucinous subtype of AIS).

- **Minimally invasive adenocarcinoma:**
- Size: <3 cm in diameter with an **invasive component of <5 mm.**
- **Invasive adenocarcinoma:**
- A tumor of any size with an **area of invasion >5 mm.**

Squamous Cell Carcinoma



- Second type of lung cancer.
- More common in **men** (unlike adenocarcinoma, which is more common in females).
- Closely correlated with **smoking** history.
    - Remember that squamous cell and small cell carcinomas have the **strongest association with smoking.**
- Location: Arise centrally in major bronchi and eventually spread to local hilar nodes but may disseminate outside the thorax.

- **Large lesions** may undergo central **necrosis**, giving rise to **cavitations**.

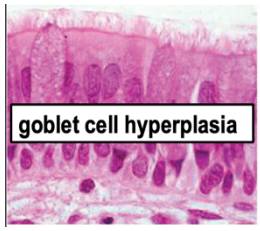
- **Preneoplastic lesions** of invasive squamous cell carcinoma:
- Squamous metaplasia or dysplasia in the bronchial epithelium.
    - Squamous cell carcinomas are preceded over years by the development of squamous metaplasia or dysplasia in the bronchial epithelium.
- This then transforms to carcinoma in situ (may last for years).
- This transforms to Squamous cell carcinoma.

- **Early stages**:
    - The lesion is **asymptomatic** in the beginning, and undetectable on radiographs.
    - **The neoplasm reaches a symptomatic stage**: When a well-defined tumor mass begins to obstruct the lumen of a major bronchus, this may be associated with distal atelectasis and infection.

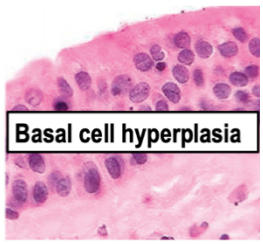
- **Morphology (Microscopically)**
  Can either be:
  1. Poorly differentiated
  2. Moderately differentiated
  3. Well differentiated

- Range from **well differentiated squamous cell neoplasms**, which show keratin pearls and intercellular bridges, to **poorly differentiated neoplasms**, with only minimal residual squamous cell features.

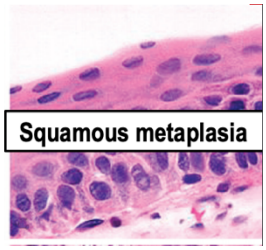
The following figures show the histologic findings of precursor lesions, CIS (Carcinoma In Situ) and Invasive Squamous Cell Carcinoma.



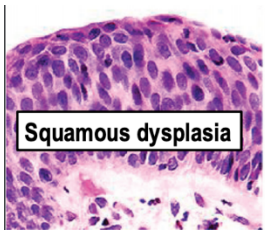
1. **Goblet cell hyperplasia:**
   One of the earliest mild changes in damaged respiratory epithelium, which results from smoking.



2. **Basal cell hyperplasia (Reserve cell hyperplasia)**
   Smoking-related adaptive response.



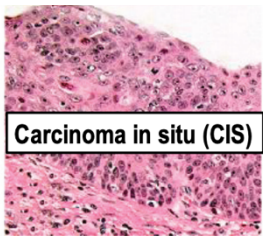
3. **Squamous metaplasia:**
   Ciliated pseudostratified columnar epithelium is replaced by squamous epithelium.
4. **Squamous dysplasia:**
   Characterized by presence of:
   a. Disordered squamous epithelium
   b. Loss of nuclear polarity
   c. Nuclear hyperchromasia
   d. Pleomorphism
   e. Mitotic figures



   May progress through stages of **mild, moderate, and severe dysplasia.**

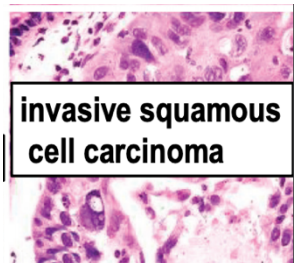
5. **Severe dysplasia (CIS):**

- Full thickness of squamous epithelium showing:
  a. Cytologic atypia
  b. Lack of basement membrane disruption
- In this stage, there is full thickness proliferation of cytologically malignant cells, without any basement membrane invasion.
- This stage happens immediately before invasive squamous cell carcinoma.



6. **Invasive Squamous Cell Carcinoma:**

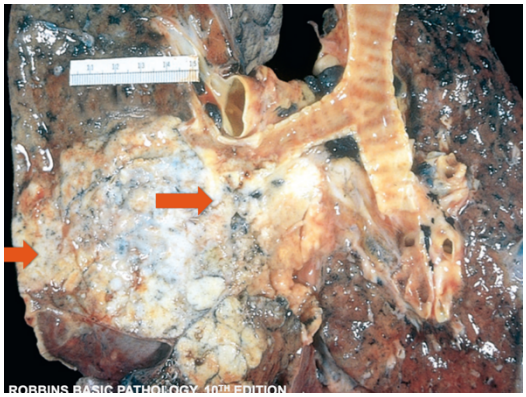
- Lesions show:
  a. Cytologic atypia
  b. Basement membrane invasion



- **Classified, according to squamous cell differentiation and cytologic features, into:**

1. Well differentiated
2. Moderately differentiated
3. Poorly differentiated

- **Gross appearance of Squamous Cell Carcinoma involving the lung.**
  There is a pale yellow-white central area, accounting for the lung carcinoma. This starts centrally and grows to the peripheral lung parenchyma.

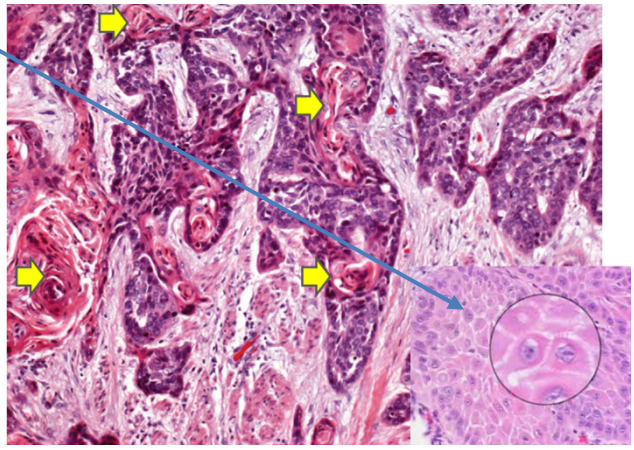


- **Histologic findings in well-differentiated squamous cell carcinoma:**

- Intercellular bridges (Desmosomes).
  The image on the bottom right (circled).

- Keratinization
  Both of the mentioned findings are features of **well-differentiation**, since normal squamous epithelium shows both.

- Presence of keratin pearls (yellow arrows).



Clinical Cases:

The parts highlighted in yellow are the clues to solving the case

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

A) Adenocarcinoma in situ
B) Squamous cell carcinoma
C) Metastatic renal cell carcinoma
D) Small cell anaplastic carcinoma

Answer: B

EXPLANATION:

- Of all lung cancers, SCC (Squamous Cell Carcinoma) is the most likely to produce paraneoplastic hypercalcemia.
- SCC is also strongly associated with smoking. (along with small cell carcinoma)
- These tumors can undergo central necrosis or **cavitation (Page 10).**
- Localized squamous cell carcinoma may be cured by surgery.

OPTION C (Renal Cell Carcinoma)

- Renal cell Carcinoma is associated with hypercalcemia, but metastatic lesions are usually **MULTIPLE** not **SOLITARY** and well circumscribed.

OPTION D (Small cell carcinoma)

- Never localized enough to be cured by surgery.
- Patients usually present in an advanced stage.
- May produce Paraneoplastic syndromes but is less likely associated with hypercalcemia.

CASE 2:

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

A) Adenocarcinoma

B) Bronchial carcinoid

C) Hamartoma

D) Squamous cell carcinoma

Answer: A

Explanation:

Glandular Differentiation: Adenocarcinomas are associated with **Acinar/Gland-forming growth patterns.**

Nonsmoker, Female: Adenocarcinomas are, by far, the **most common primary tumors arising in women, and in people who have never smoked.**

GOOD LUCK