Reparatory system lectures 8-10

Heyam Awad

note

These lectures cover the following topics

1. Diffuse hemorrhagic syndromes
2. Lung tumors

important: theses slides are your study source for these lectures. there is no handout for these. the slides are detailed and are enough for the exam.

Diffuse alveolar hemorrhagic syndromes

- These are a group of primary immune – mediated diseases that manifest as hemoptysis, anemia and diffuse pulmonary infiltrates.
- These diseases include the following entities:

1. Goodpasture syndrome
2. idiopathic pulmonary hemosiderosis

Goodpasture syndrome

-this is an uncommon , rapidly progressive, glomerulonephritis and hemorrhagic interstitial pneumonitis.

- Both the renal and the pulmonary lesions are caused by **antibodies targeted against the noncollagenous domain of the α3 chain of collagen IV which can be detected in the serum of more than 90% of patients**
- **So this is an example of type 2 hypersensitivity reaction.**

- Note that in type 2 hyprsensitivity the antibodies are deposited in tissues and they cause damage by several mechanisms including opsonization and phagocytosis, inflammation through complement fixation or direct cellular dysfunction.

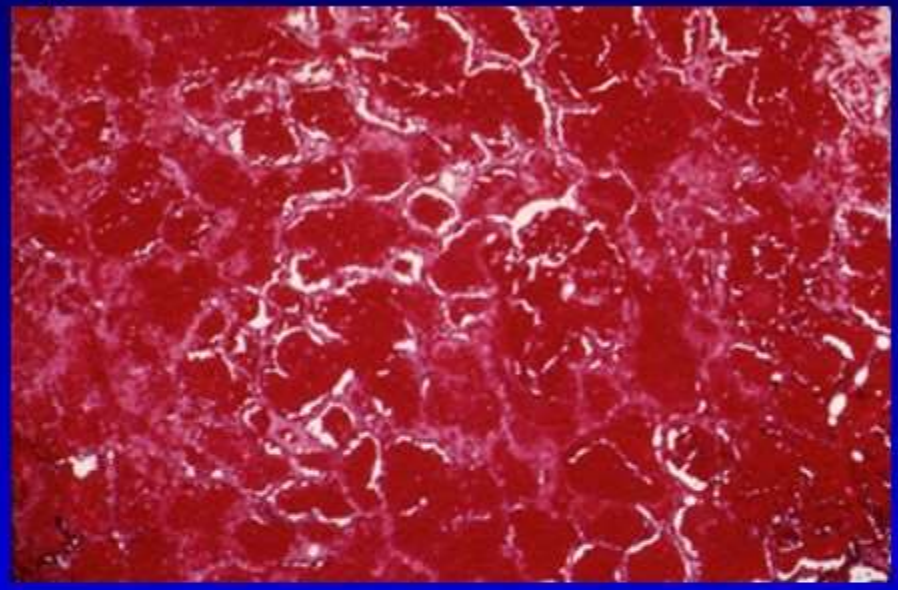
- In Goodpasture syndrome the antibodies activate complement by the classical pathway. This triggers an inflammatory reaction.

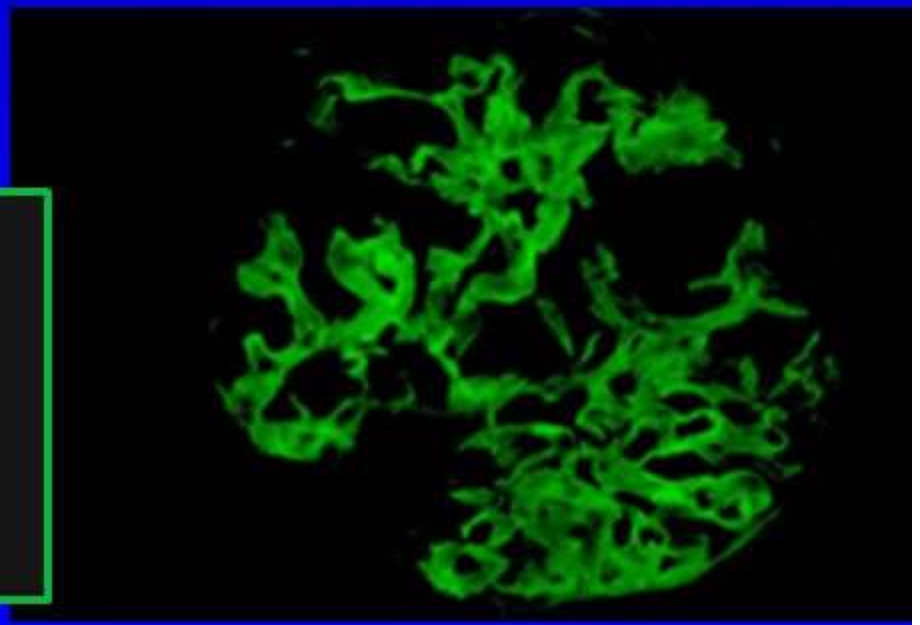
morphology

- The lungs are heavy with red brown consolidation due to diffuse hemorrhage within the alveoli.
- Microscopy shows necrosis of alveolar walls and associated alveolar hemorrhage.

Goodpasture syndrome

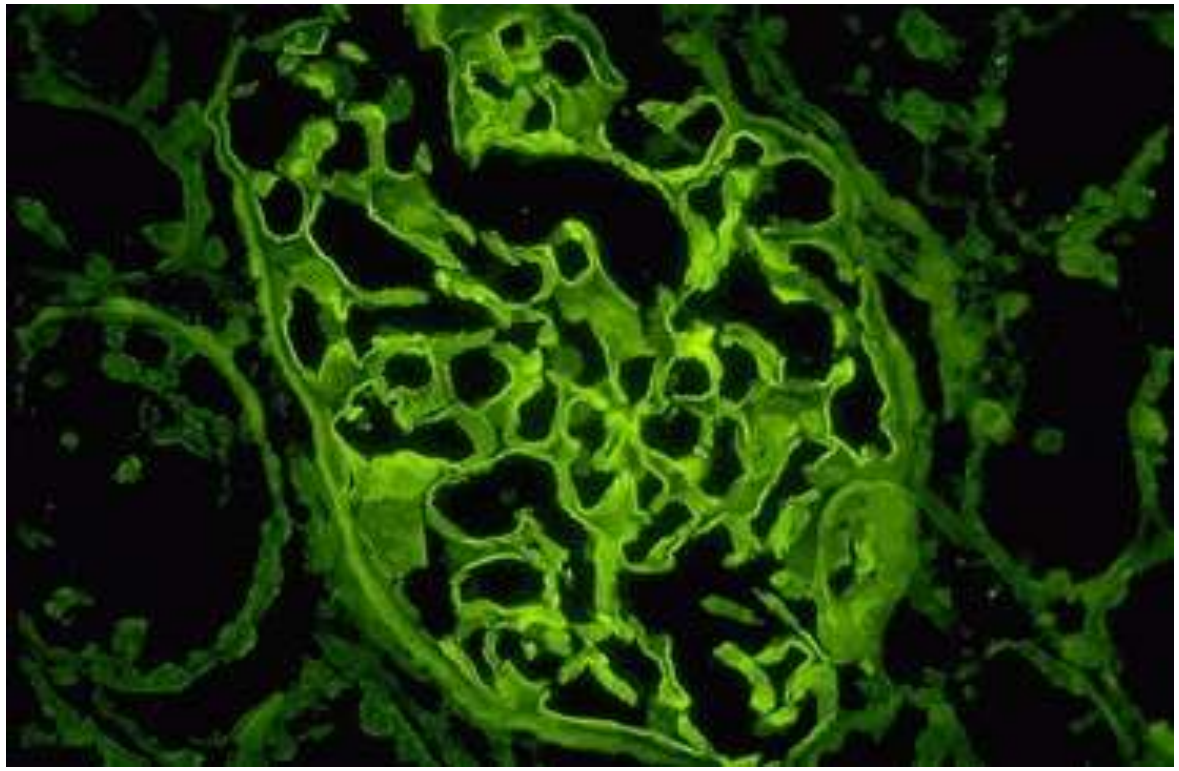
Iron stain in sputum





Immunofluorescence of renal biopsy staining for IgG in a linear pattern in patient with anti-glomerular basement membrane (anti-GBM) disease

Linear IgG



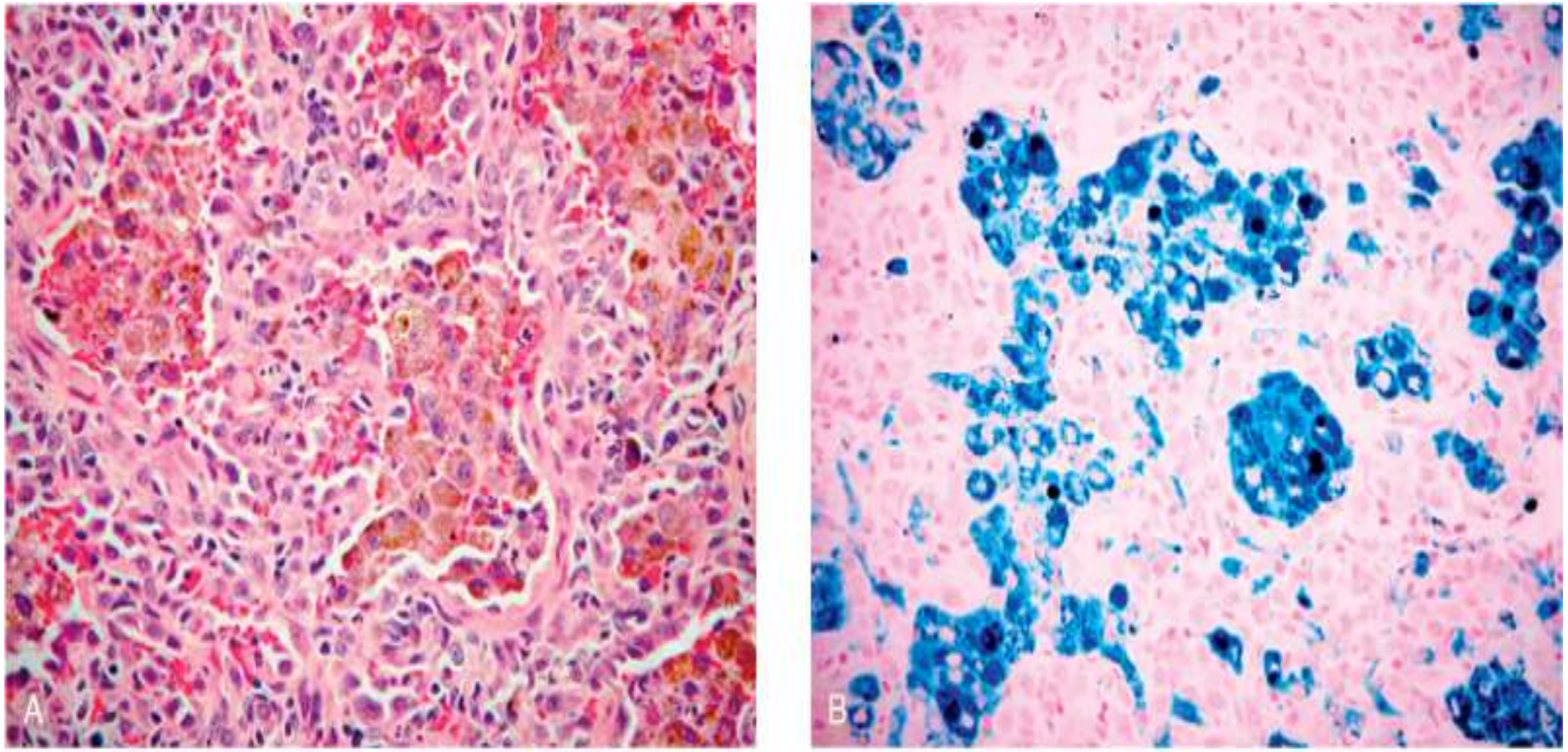
- The characteristic linear pattern of immunoglobulin deposition (usually IgG, that is the hallmark diagnostic finding in renal biopsy specimens may be seen along the alveolar septa by immunoflurescence studies.
- Plasmapheresis which removes the offending agent and immunosuppressive therapy that inhibits antibody formation have markedly improved the prognosis
- With severe renal disease, renal transplantation is eventually required

Idiopathic Pulmonary Hemosiderosis

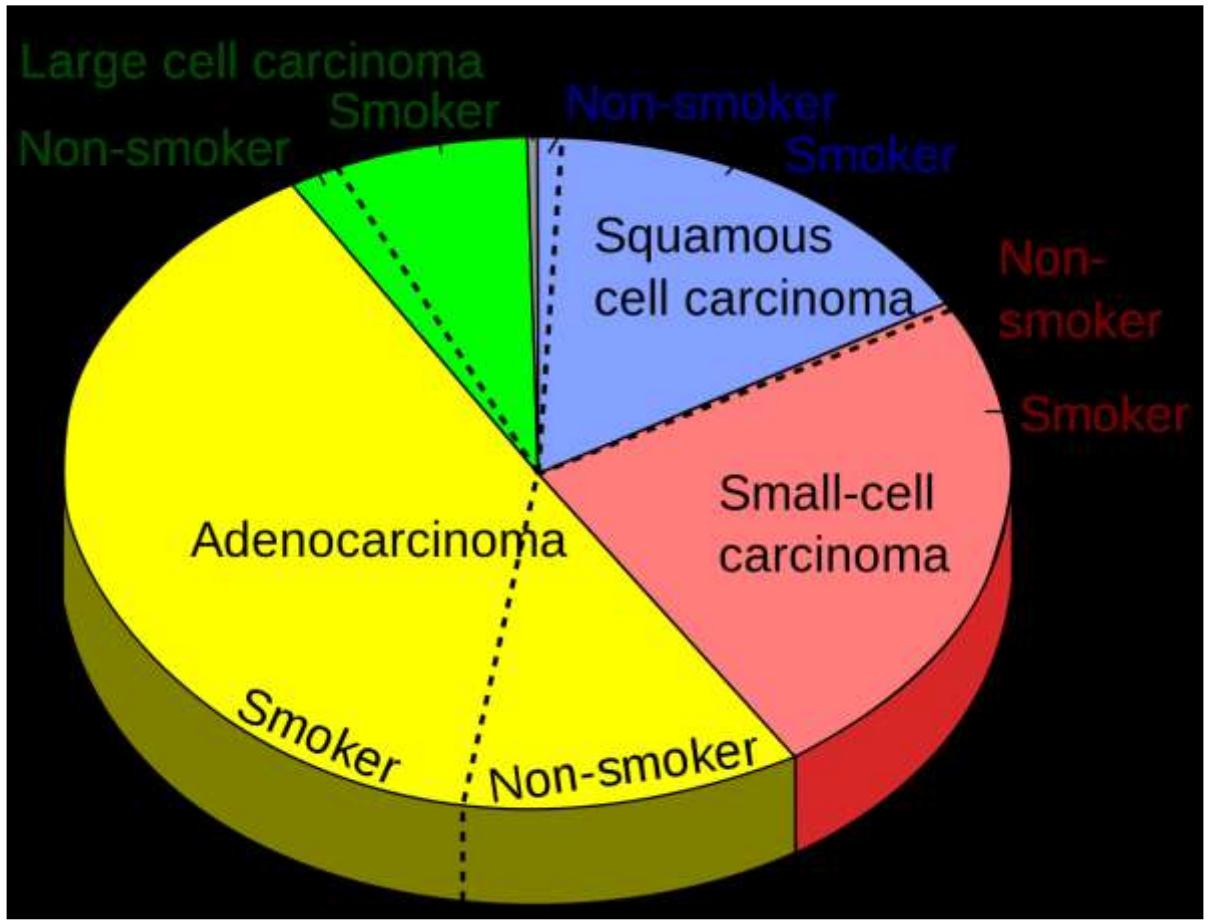
similar to Goodpasture syndrome but

- a. No associated renal disease
- b. No circulating anti-basement membrane antibody.
- Most cases occur in children, although the disease is reported in adults as well, who have a better prognosis
- With steroid and immunosuppressive therapy, survival has markedly improved from the historical 2.5 years;
- thus, an immune-mediated etiology is postulated

Diffuse alveolar hemorrhage syndrome –perl'sstain(an iron stain)



Lung carcinoma



Lung cancer

- Lung tumors can be primary or secondary (metastasis)
- Primary lung cancer is a relatively common disease .
- 95% of primary lung tumors are carcinomas, the remaining include other tumors like: carcinoid, lymphomas, mesenchymal tumors like fibrosarcoma and leiomyosarcoma.
- lung 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 poor:
- 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
- a. Adenocarcinoma
- b. Squamous cell carcinoma (SCC)
- c. Small cell carcinoma,
- d. Large cell carcinoma

- Carcinomas of the lung were classified into two groups:
- a. Small cell lung cancer (SCLC) and .. These are neuroendocrine tumrs.
- 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 respectable 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.

- 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 procarcinogens derived from cigarette smoke, and thus have the greatest risk for development of 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
- 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

- Among the major histologic subtypes of lung cancer, squamous and small-cell carcinomas show the strongest association with tobacco exposure.

- This is because smoking causes **squamous metaplasia** that progresses to dysplasia then carcinoma.

- 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.

Mutations in lung cancer include (no need to memorize these)

- 1. Inactivation of tumor suppressor genes located on the short arm of chromosome 3
- 2. TP53 mutations or activation of the KRAS are common in lung cancer.
- 3. 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 fusion genes and

- The specific mutations in adenocarcinoma mentioned in the previous slide, while rare, 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

1. Squamous cell carcinomas :

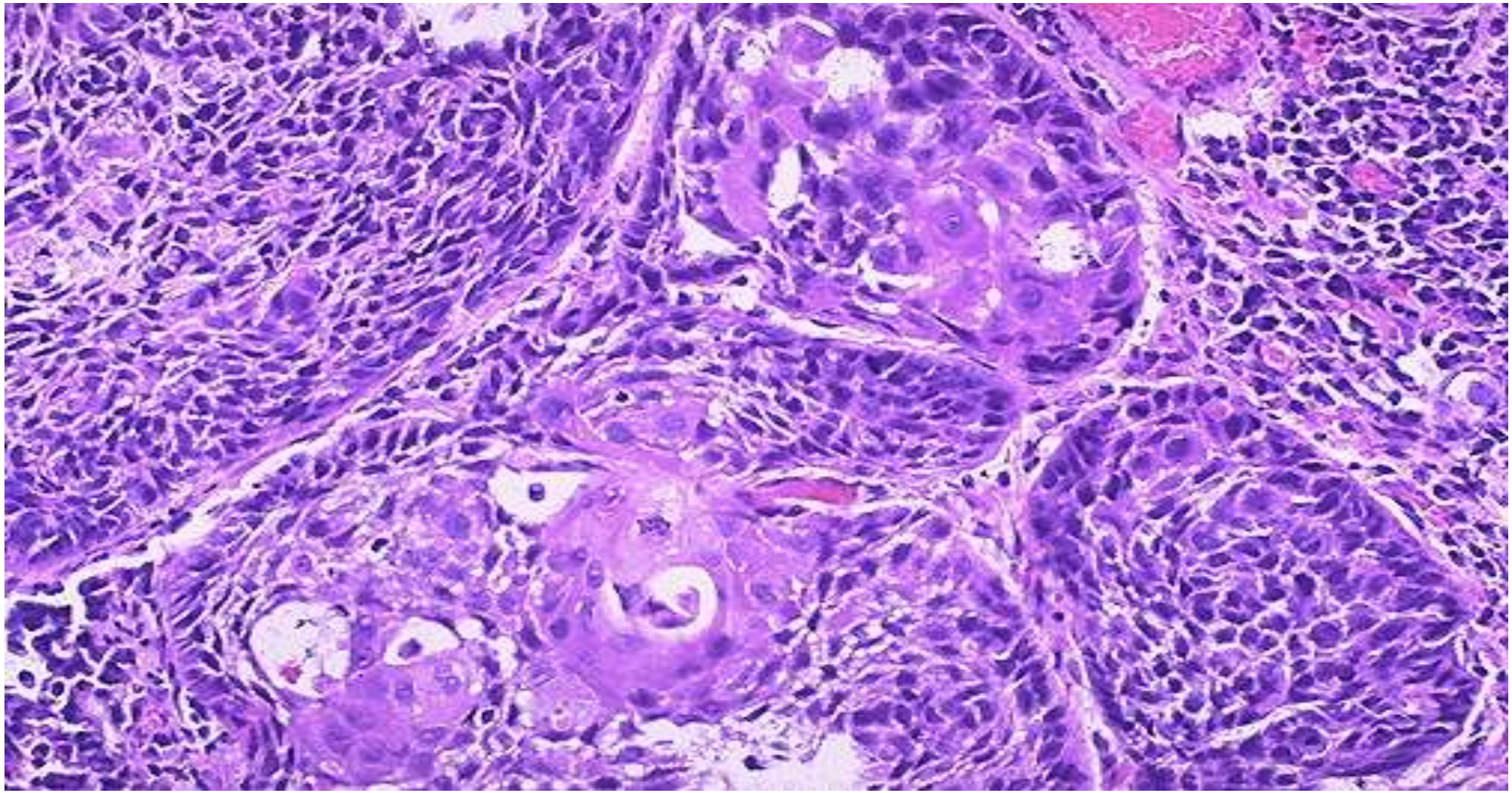
a. Are more common in men than in women

b. Are closely correlated with a smoking history;

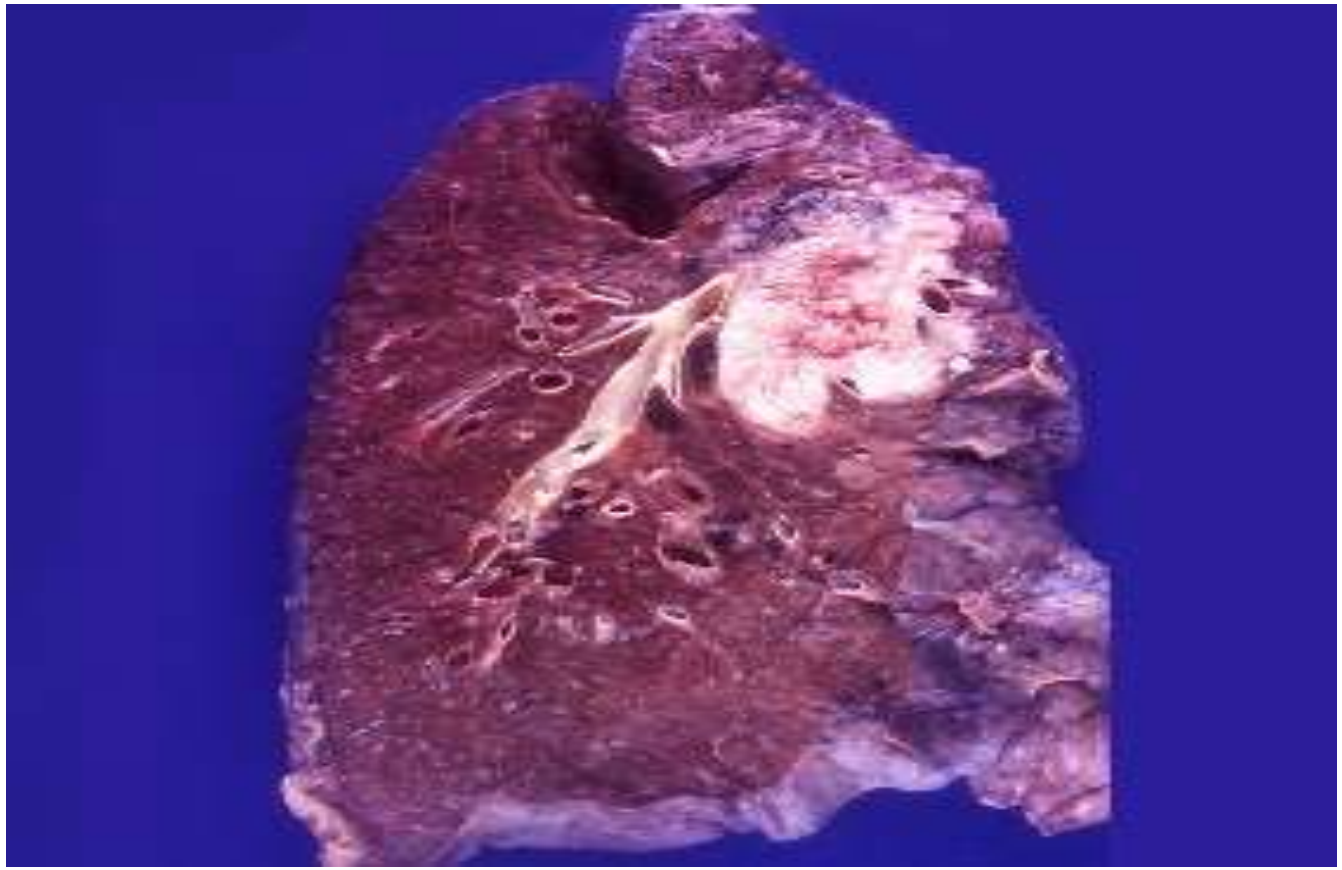
c. They tend to arise centrally in major bronchi and eventually spread to local hilar nodes,

d. Disseminate outside the thorax later than do other histologic types

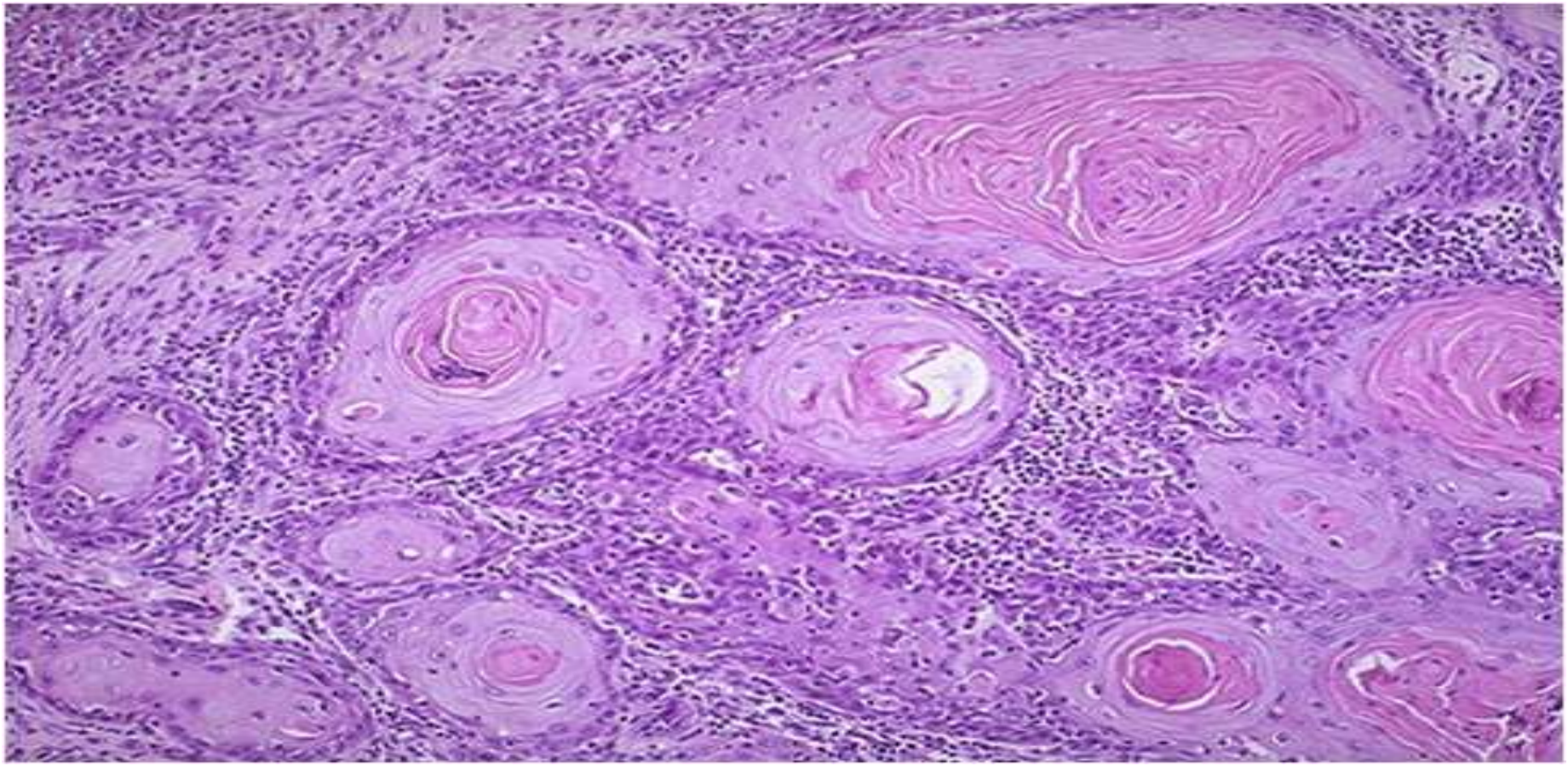
Squamous cell carcinoma of lung



SCC.. Centrally located



SCC.. Keratin production



2. Adenocarcinomas:

a. May occur as central lesions but usually are more

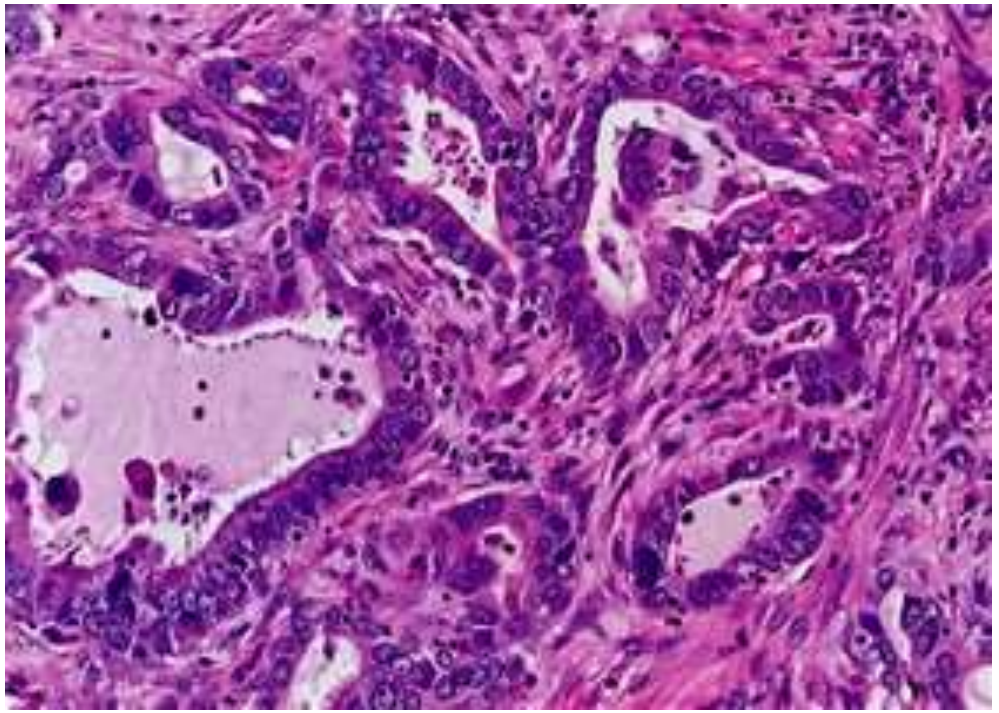
peripherally located, many with a central scar.

b. Are the most common type of lung cancer in women and nonsmokers

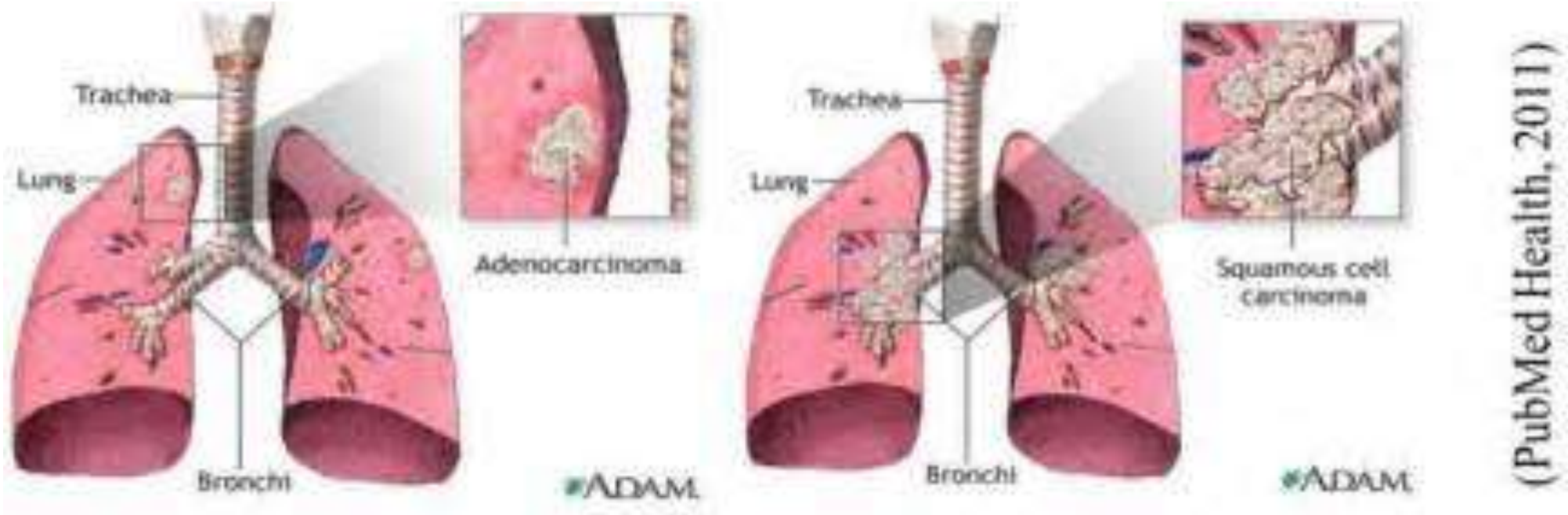
c. In general, adenocarcinomas grow slowly and form smaller masses than do the other subtypes

d. They tend to metastasize widely at an early stage

Adenocarcinoma: tumor forming glandular structures



Note: adenocarcinoma is usually peripherally located, squamous usually centrally located.



3. Small cell lung carcinomas (SCLCs) are:

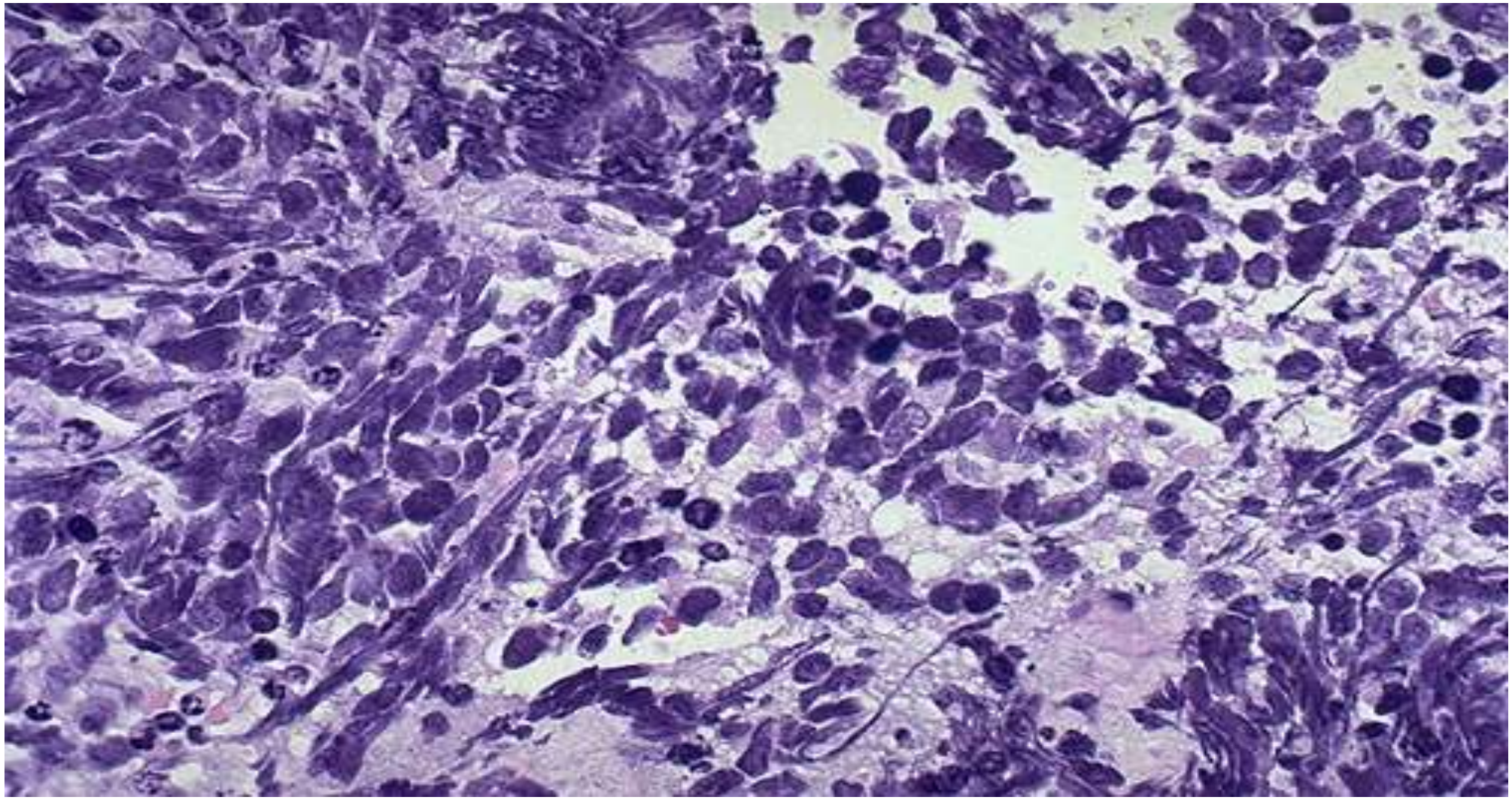
a. Centrally located with extension into the lung parenchyma

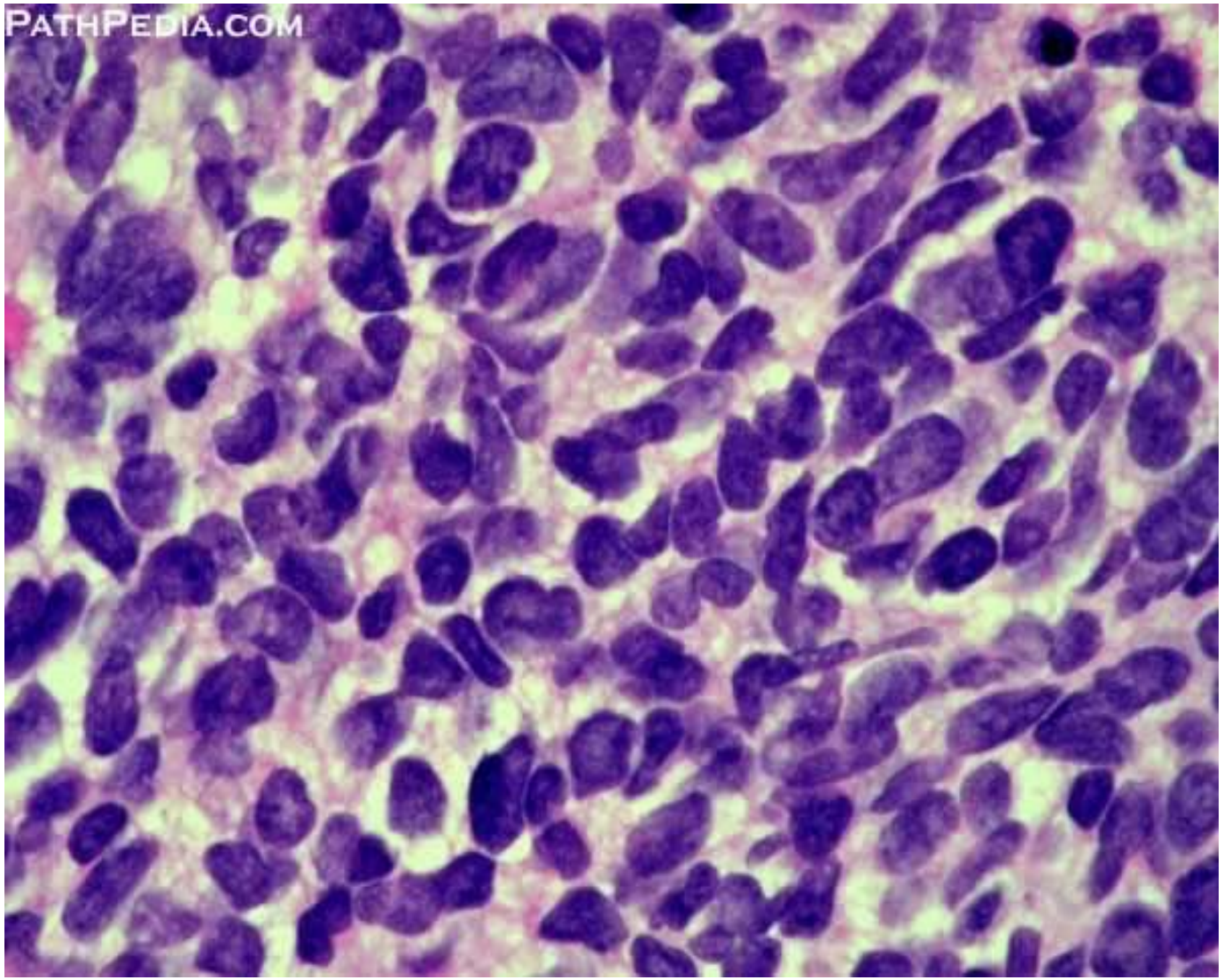
b. Early involvement of the hilar and mediastinal nodes.

c. Are composed of tumor cells with a round shape, scant cytoplasm, and finely granular chromatin with many mitotic figures .

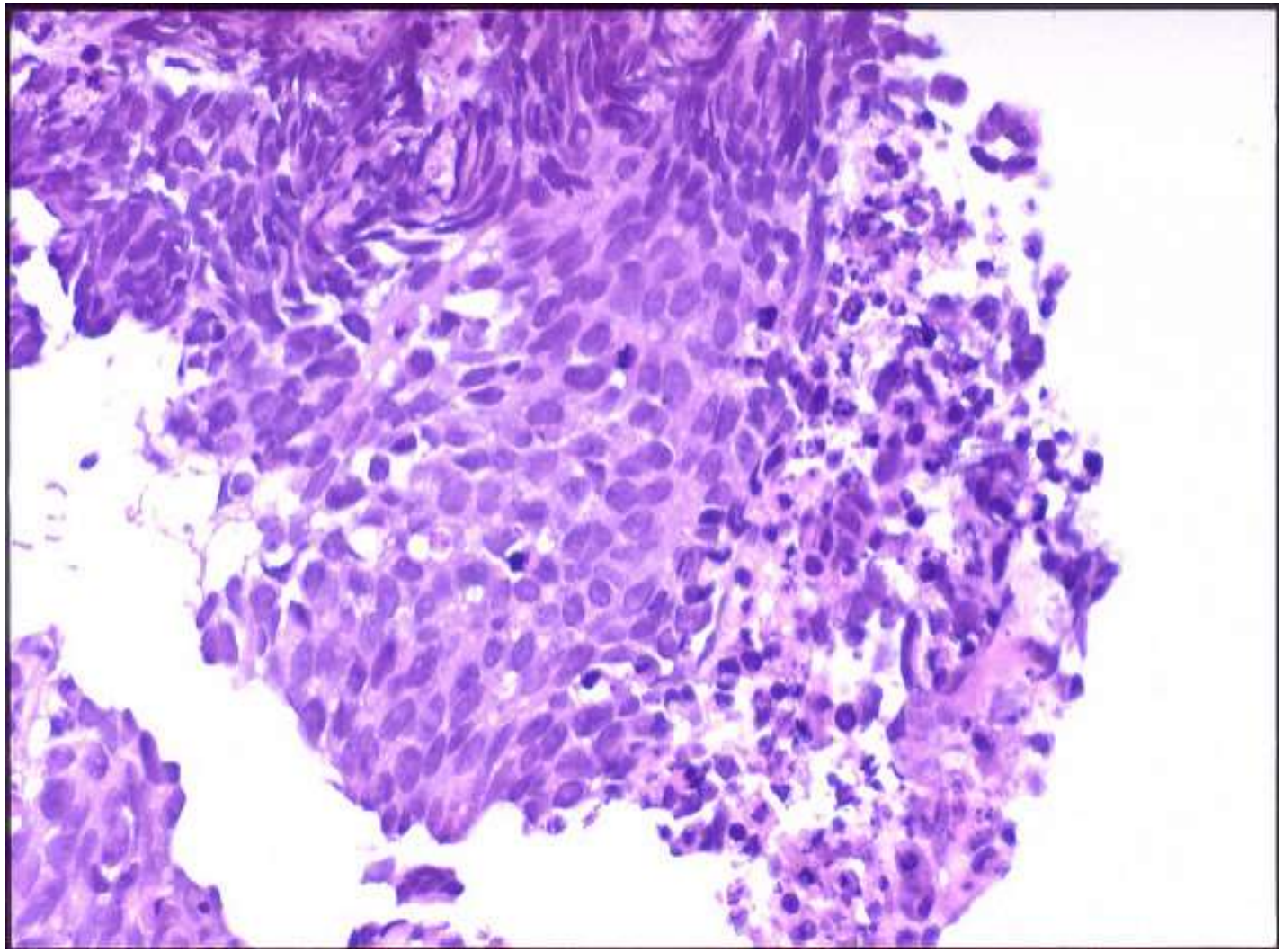
- Necrosis is invariably present and may be extensive
- Fragile cells that show fragmentation and "**crush artifact".**
- Nuclear molding resulting from close apposition of tumor cells that have **scant cytoplasm**.

Small cell carcinoma of the lung




PATHPEDIA.COM

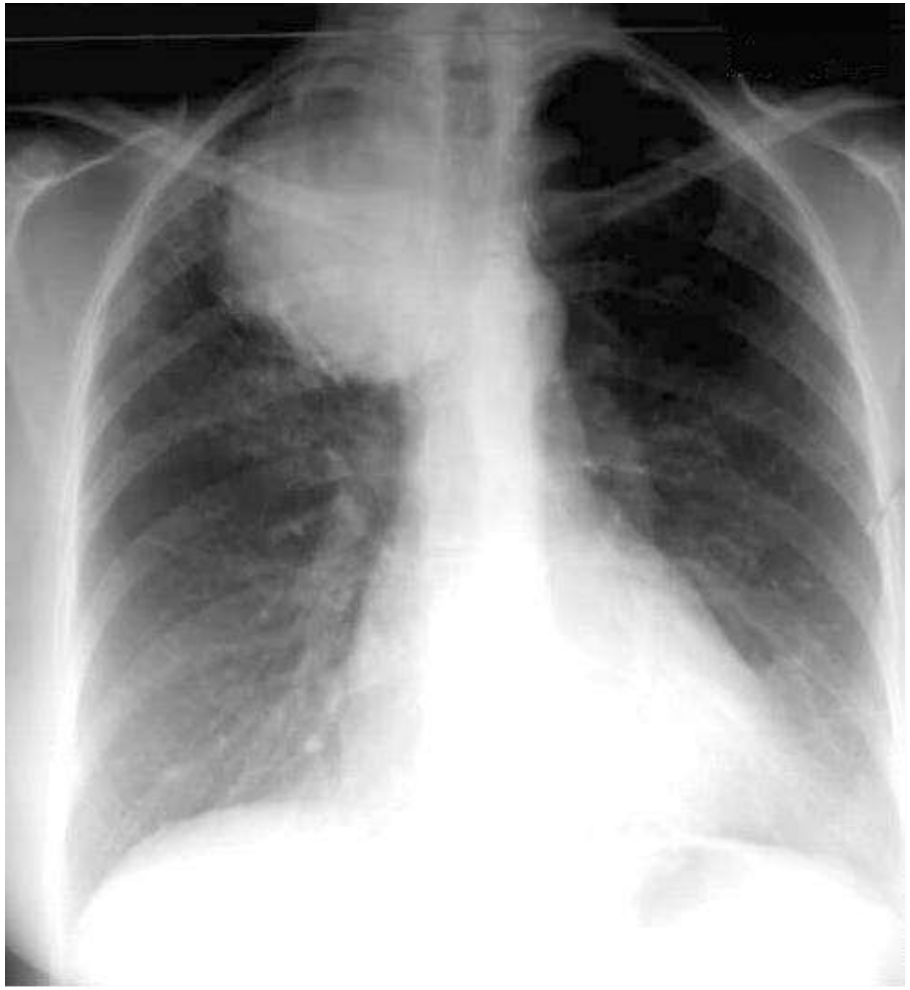
Crushing artefacts in small cell carcinoma



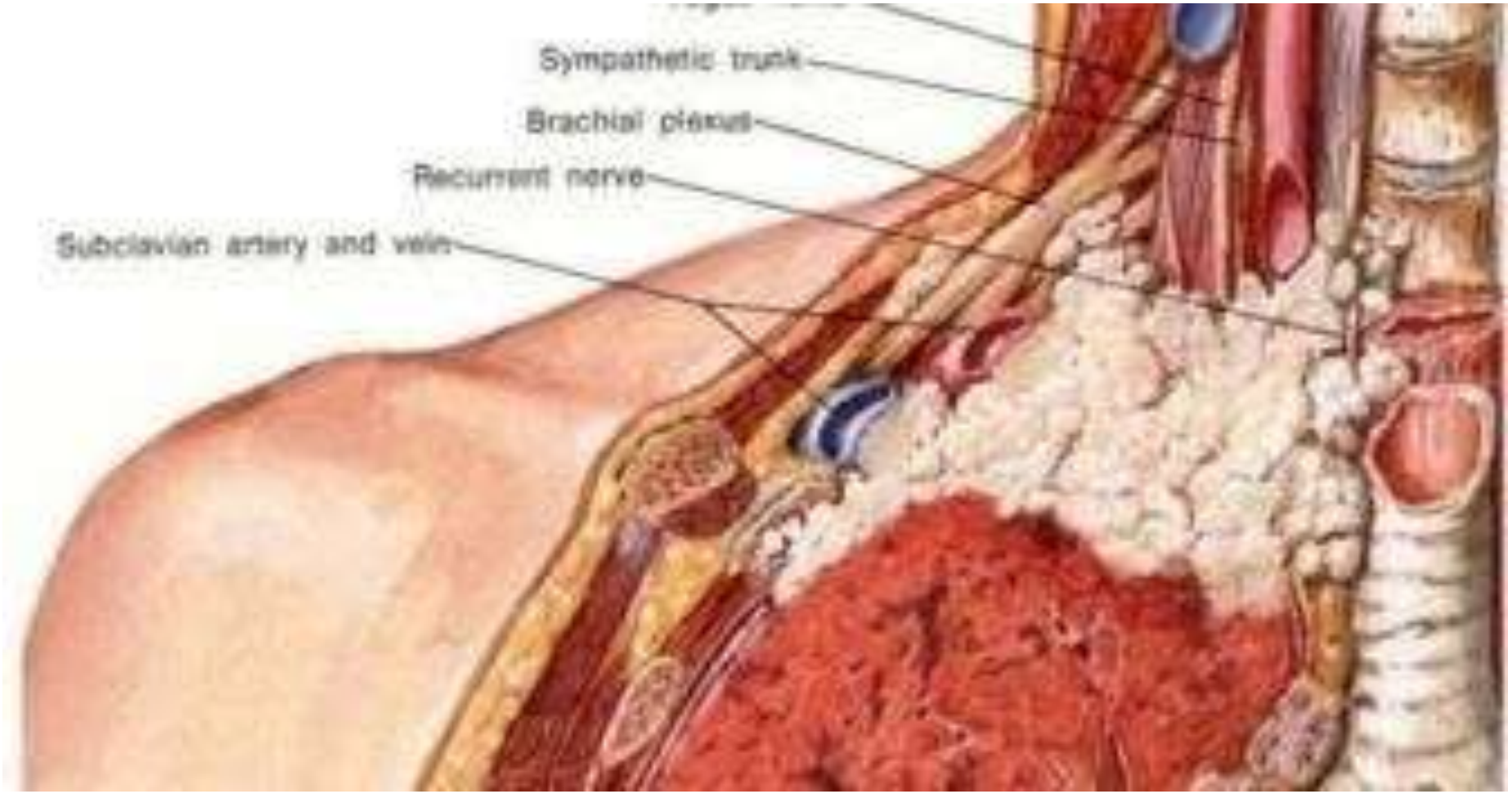
Pancoast tumor

- Apical lung neoplasms are called Pancoast tumors.
- These can be of any histological pattern.
- They can invade the brachial or cervical sympathetic plexus and cause severe pain in the distribution of the ulnar nerve.

Pancoast tumor



Pancoast tumor



Clinical Course of lung cancer

- 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 lung cancer develop clinically overt paraneoplastic syndromes.

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

Carcinoid tumors

- These are malignant tumors composed of cells of neuroendocrine origin.
- They might secrete hormones.. Rarely
- They are resectable and curable.

- Please note that small cell carcinoma is also neuroendocrine in origin, but small cell has a very bad prognosis whereas carcinoid tumors have a much better prognosis.


THANK YOU!