Respiratory system lecture 7-9 part 1

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FRCPath

sarcoidosis

- Granulomatous disease that affects many organs.
- In the lungs, sarcoidosis causes restrictive lung disease.

- Although sarcoidosis is an example of a restrictive lung disease, **it is important to note that sarcoidosis is a multisystem disease of unknown etiology characterized by noncaseating granulomas in many tissues and organs**.

- Other diseases, including mycobacterial or fungal infections may also produce noncaseating granulomas; so the histologic ***diagnosis of sarcoidosis is one of exclusion***.

Epidemiology

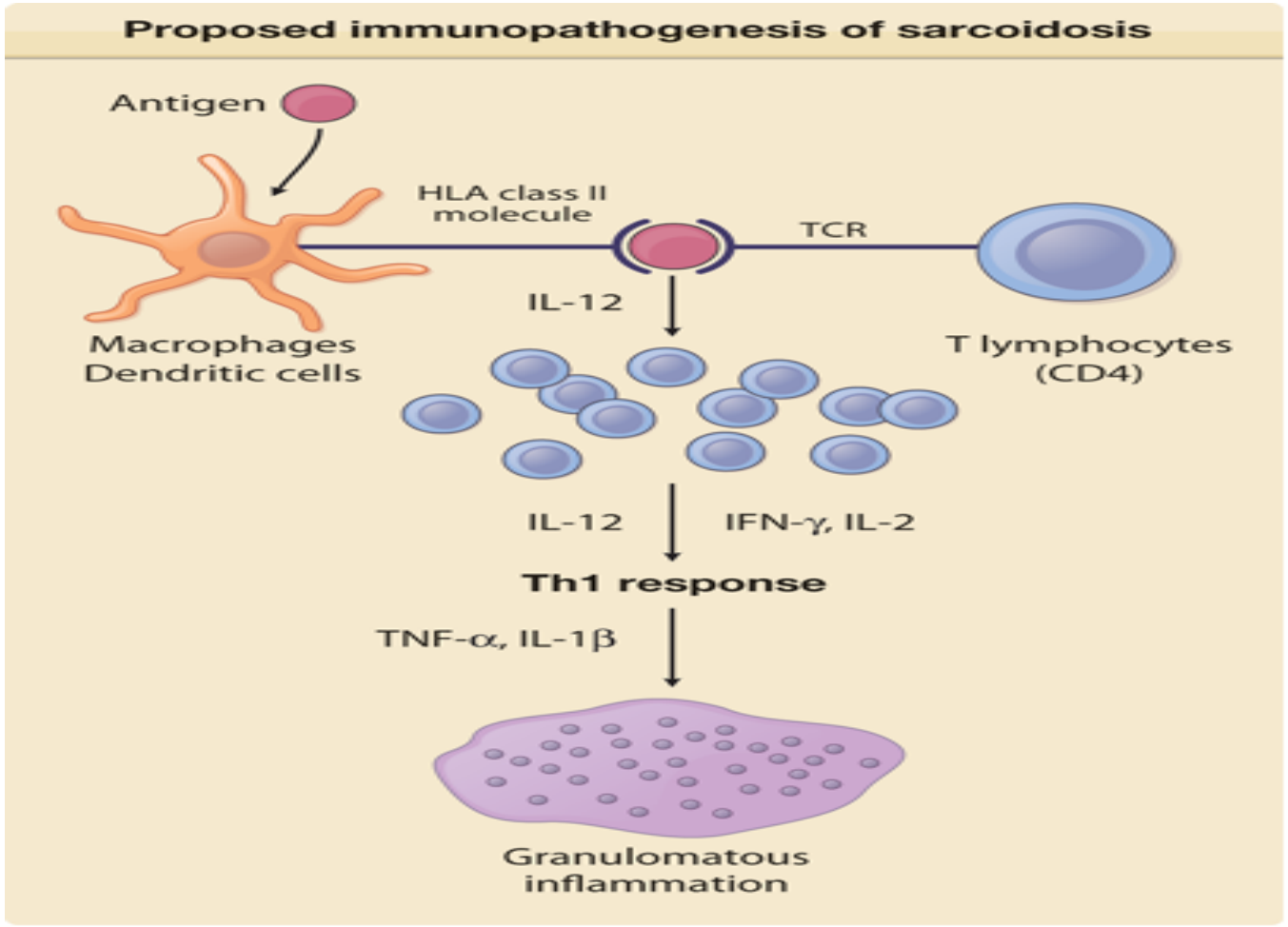
- It occurs throughout the world, affecting both genders and all races and age groups.
- There is a consistent predilection for adults younger than 40 years of age
- A high incidence has been noted among African Americans
- Sarcoidosis is one of the few pulmonary diseases with a higher prevalence among nonsmokers.

ETIOLOGY AND PATHOGENESIS

- etiology of sarcoidosis is unknown, but several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed persons exposed to certain environmental agents

- Immunologic abnormalities in sarcoidosis suggest the development of a cell-mediated response to an unidentified antigen and the process is driven by CD4+ helper T cells. These abnormalities include:

1. Intra-alveolar and interstitial accumulation of CD4+ T_H1 cells
2. Increases in T cell-derived T_H1 cytokines such as IL-2 and IFN-γ, resulting in T cell expansion and macrophage activation, respectively
3. Anergy to common skin test antigens such as purified protein derivative (PPD), that may result from pulmonary recruitment of CD4+ T cells and consequent peripheral depletion



Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

- The role of genetic factors is suggested by

a. Familial clustering of cases and

b. Association with certain human leukocyte antigens (HLA) (class I HLA-A1 and HLA-B8)

- After lung transplantation, sarcoidosis recurs in the new lungs in 75% of patients.

- **MORPHOLOGY**

- The diagnostic histopathologic feature of sarcoidosis is the **noncaseating epithelioid granuloma**, irrespective of the organ involved

Two other microscopic features are sometimes seen:

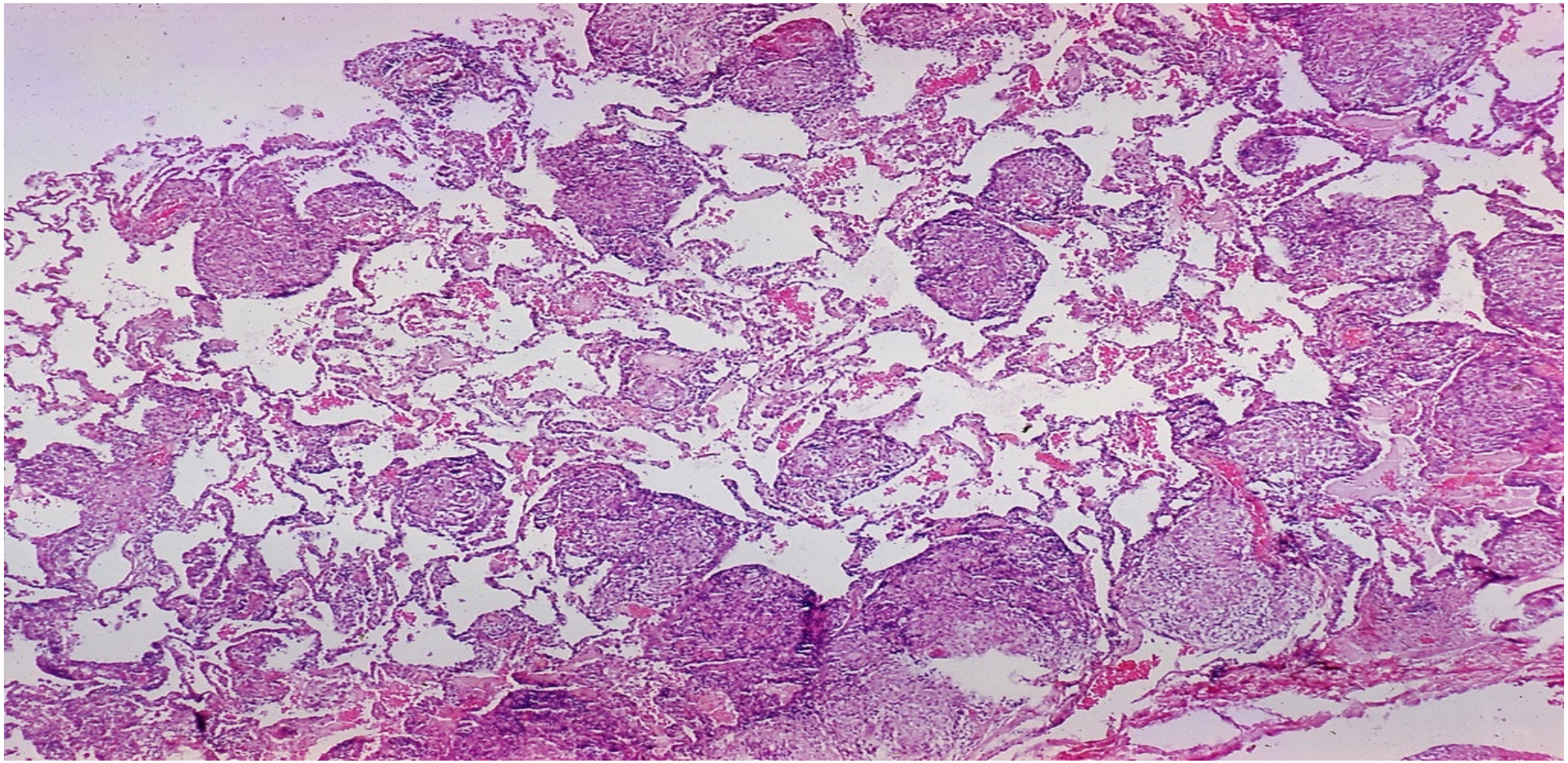
1. **Schaumann bodies**, laminated concretions composed of calcium and proteins

- 2. **Asteroid bodies**, stellate inclusions enclosed within giant cells. .

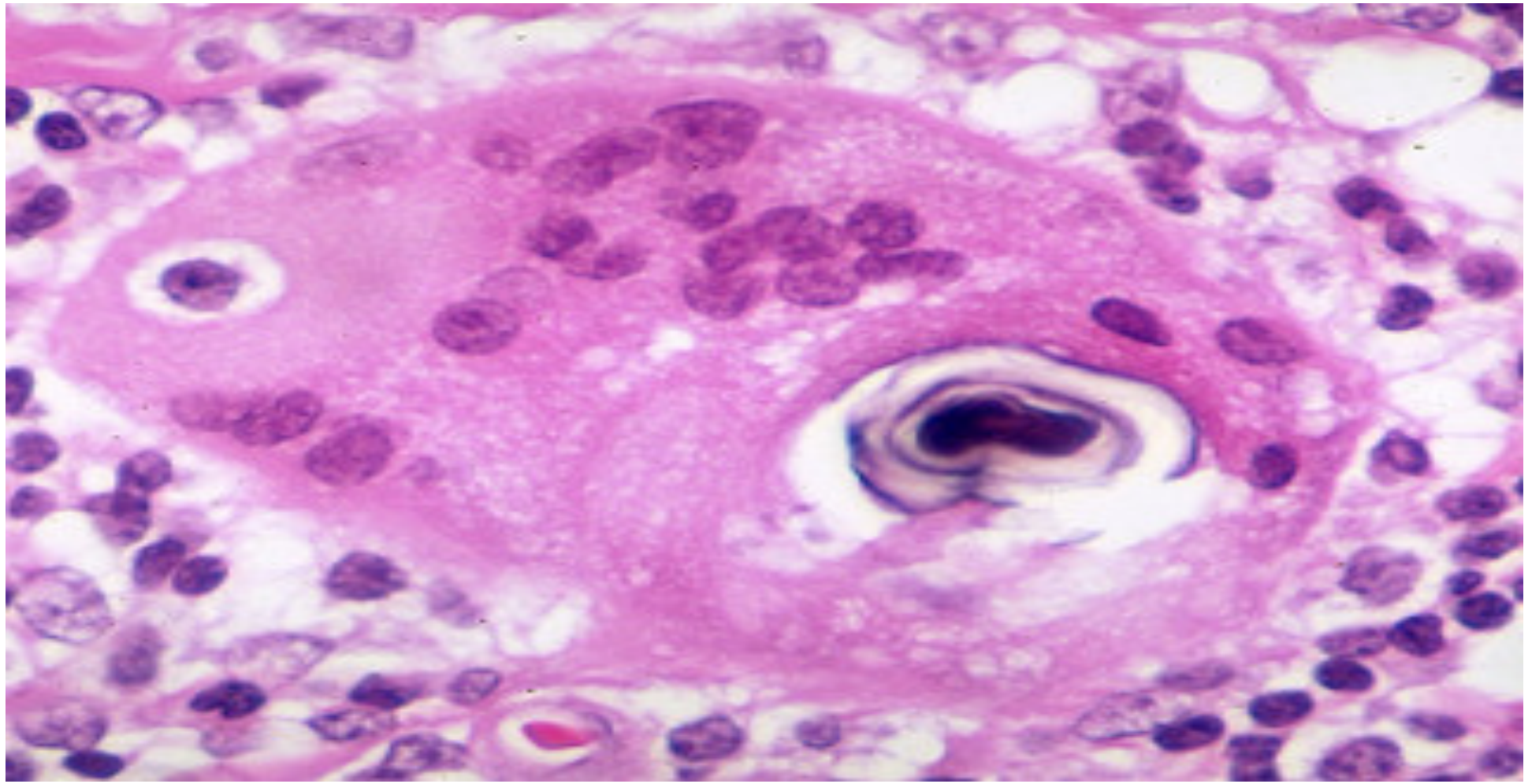
- (1&2) above are not required for diagnosis of sarcoidosis-they also may occur in granulomas of other origins.

- Caseation necrosis typical of tuberculosis is absent

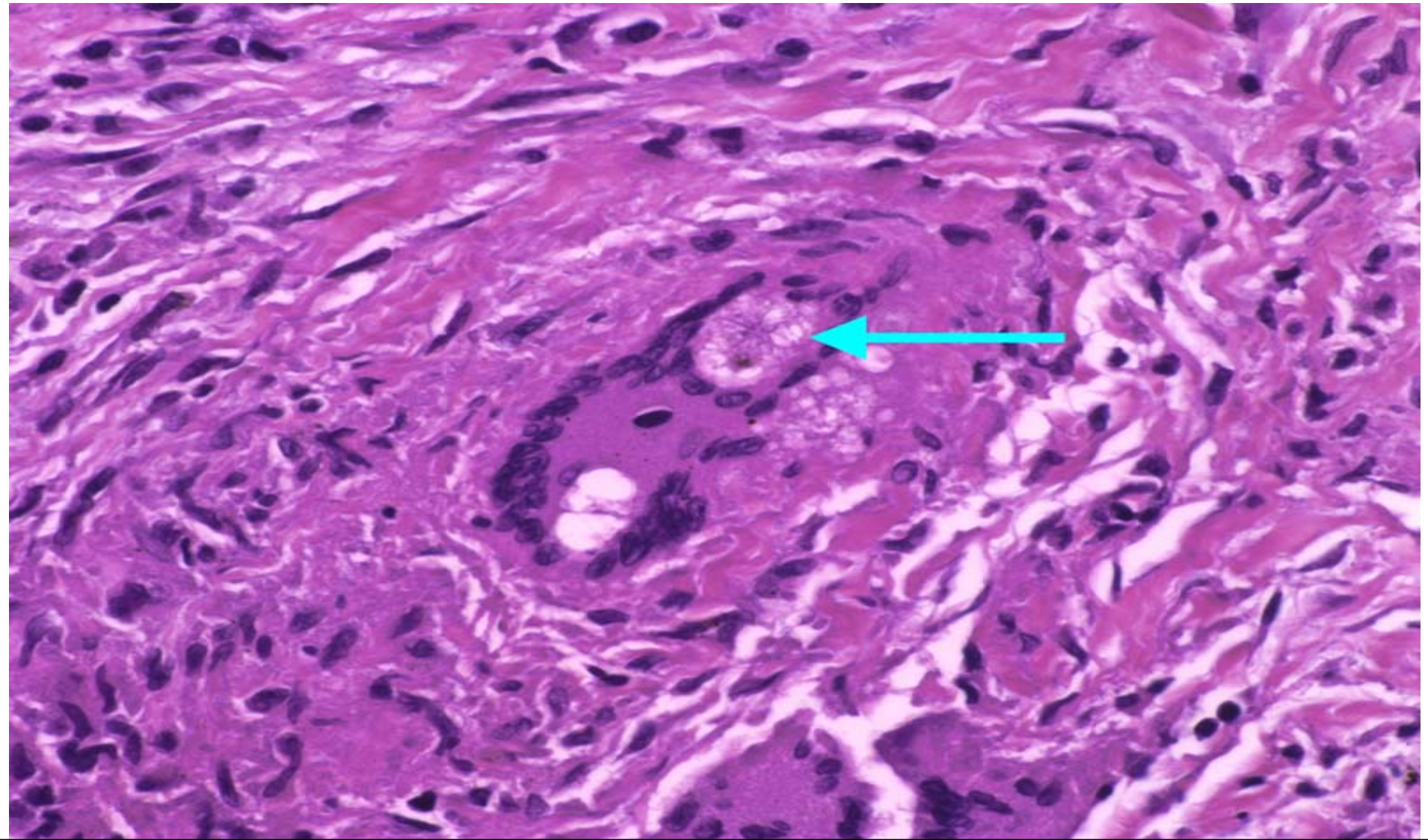
sarcoidosis



Shaumann bodies: laminated concretions composed of calcium and proteins



Asteroid bodies: stellate inclusion within giant cells



Involved organs:

1. The **lungs** are involved at some stage of the disease in 90% of patients:

- The granulomas predominantly involve the interstitium rather than air spaces, with some tendency to localize in the connective tissue around bronchioles and venules and in the pleura

2. Intrathoracic hilar and paratracheal lymph nodes are enlarged in 75% to 90% of patients, while a third present with peripheral lymphadenopathy.

3. Skin lesions are encountered in approximately 25% of patients:

a.Erythema nodosum,

- The hallmark of acute sarcoidosis, consists of raised, red, tender nodules on the anterior aspects of the legs.
- Sarcoidal granulomas are uncommon in these lesions.

b. Subcutaneous nodules

- Are discrete and painless
- These usually reveal abundant noncaseating granulomas.

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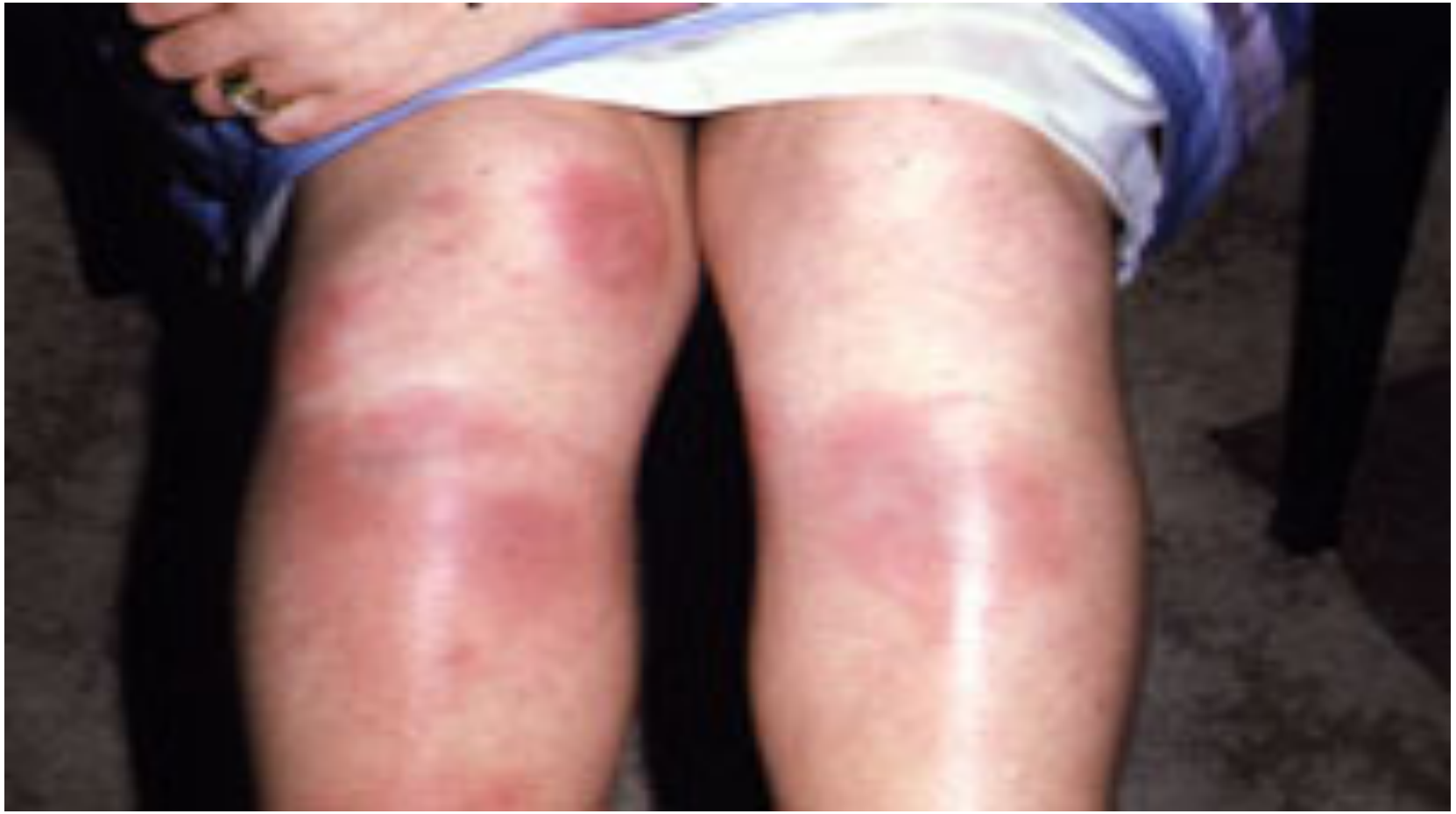
Erythema Nodosum



4. Involvement of the eye and lacrimal glands occurs in about one fifth to one half of patients and the ocular involvement takes the form of iritis or iridocyclitis and may be unilateral or bilateral-

-As a consequence, corneal opacities, glaucoma, and (less commonly) total loss of vision may develop.

- These ocular lesions are frequently accompanied by inflammation in the lacrimal glands, with suppression of lacrimation (sicca syndrome).

5. Unilateral or bilateral parotitis with painful enlargement of the parotid glands

- Some patients develop xerostomia (dry mouth).

Note:

- Combined uveoparotid involvement is designated **Mikulicz syndrome**.

Clinical Features

-In many persons the disease is asymptomatic and discovered on routine chest films as bilateral hilar adenopathy or as an incidental finding at autopsy.

- In others, peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly may be presenting manifestations.

- In about two thirds of symptomatic cases, there is gradual appearance of respiratory symptoms (shortness of breath, dry cough, or vague substernal discomfort) or constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats

***Note*:**

- Other findings include hypercalcemia and is not related to bone destruction but rather are caused by increased calcium absorption secondary to production of **active vitamin D by the mononuclear phagocytes in the granulomas.**

Clinical course:

- Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periods of activity interspersed with remissions.

- The remissions may be spontaneous or initiated by steroid therapy and often are permanent.
- Overall, 65% to 70% of affected persons recover with minimal or no residual manifestations.
- Another 20% develop permanent lung dysfunction or visual impairment.
- Of the remaining 10% to 15%, most succumb to progressive pulmonary fibrosis and cor pulmonale.

Hypersensitivity pneumonitis

- A granulomatous disease that can cause restrictive lung disease

Hypersensitivity pneumonitis = allergic alveolitis

- A granulomatous disease that can cause restrictive lung disease
- Immunologically mediated
- Causative agent: known!!.. Usually occupational

- Hypersensitivity pneumonitis

  Is an immunologically mediated inflammatory lung disease that primarily affects the alveoli and is often called allergic alveolitis.

- Most often it is an occupational disease that results from sensitivity to inhaled antigens such as in moldy Hay .

- The occupational exposures are diverse, but the syndromes share common clinical and pathologic findings and probably have a very similar pathophysiologic basis

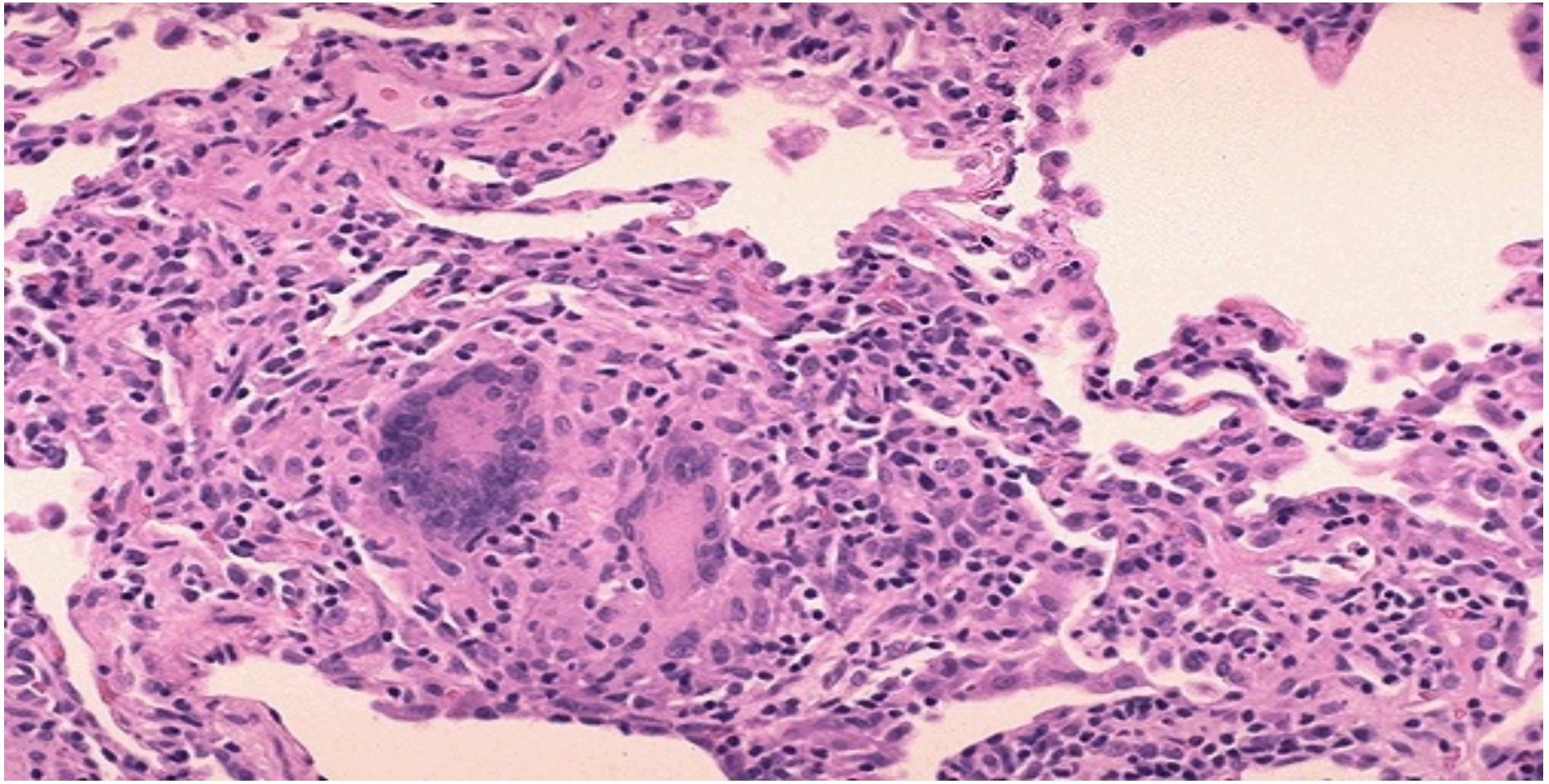
syndrome	exposure	antigen	
Farmer's lung	Moldy hay	micropolyspora	
Maple bark disease	Moldy maple bark	cryptostroma	
Pigeon breeder's lung	Pigeon droppings	Pigeon serum protein	

diagnosis

- With the acute form of this disease, the diagnosis is usually obvious because of the temporal relationship of symptom onset to exposure to the incriminating antigen.
- Can present as a chronic disease characterized by insidious onset of cough, dyspnea, malaise, and weight loss.

- If antigenic exposure is terminated after the acute attacks, complete resolution of pulmonary symptoms occurs within days
- Failure to remove the inciting agent eventually results in an irreversible chronic interstitial pulmonary disease

Hypersensitivity Pneumonitis



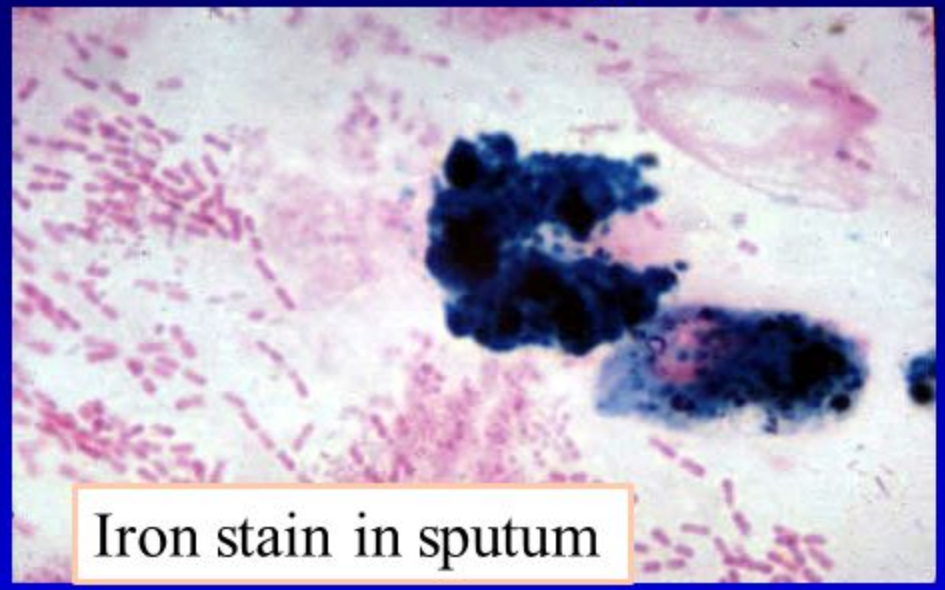
Diffuse alveolar hemorrhagic syndromes

- 1. Goodpasture syndrome

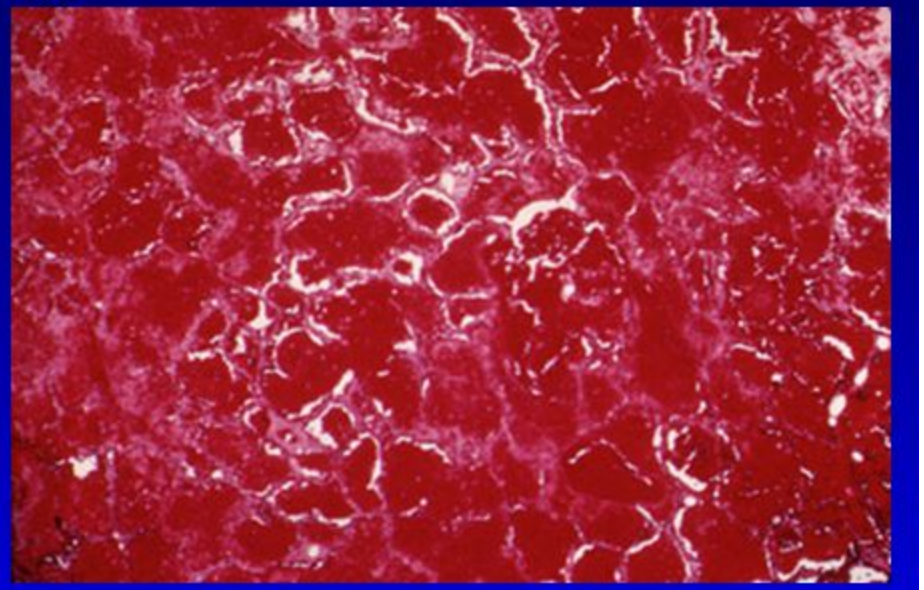
uncommon , rapidly progressive, glomerulonephritis and hemorrhagic interstitial pneumonitis.

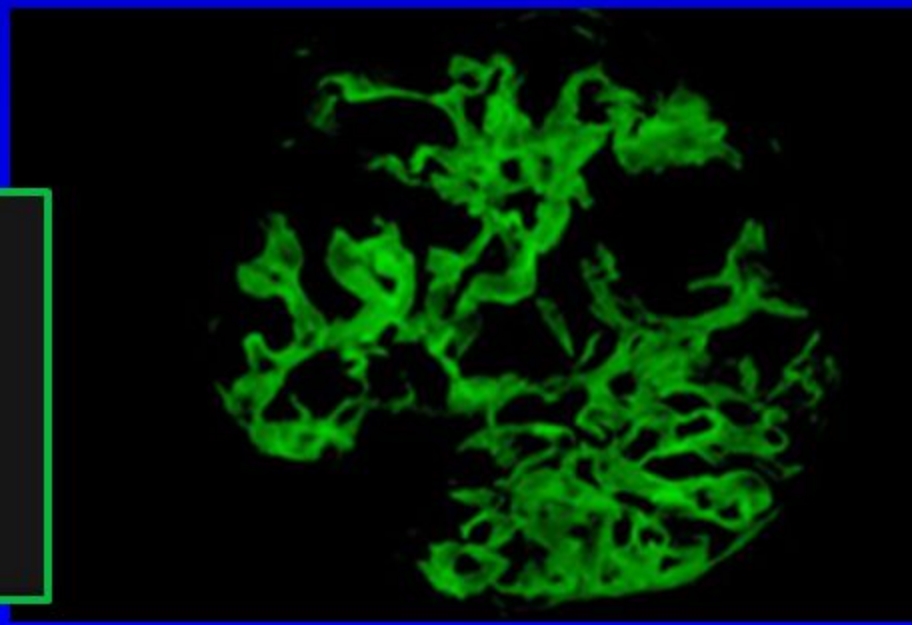
- Both the renal and the pulmonary lesions are caused by **antibodies targeted against the noncollagenous domain of the α3 chain of collagen IV which can be detected in the serum of more than 90% of patients**

Goodpasture syndrome

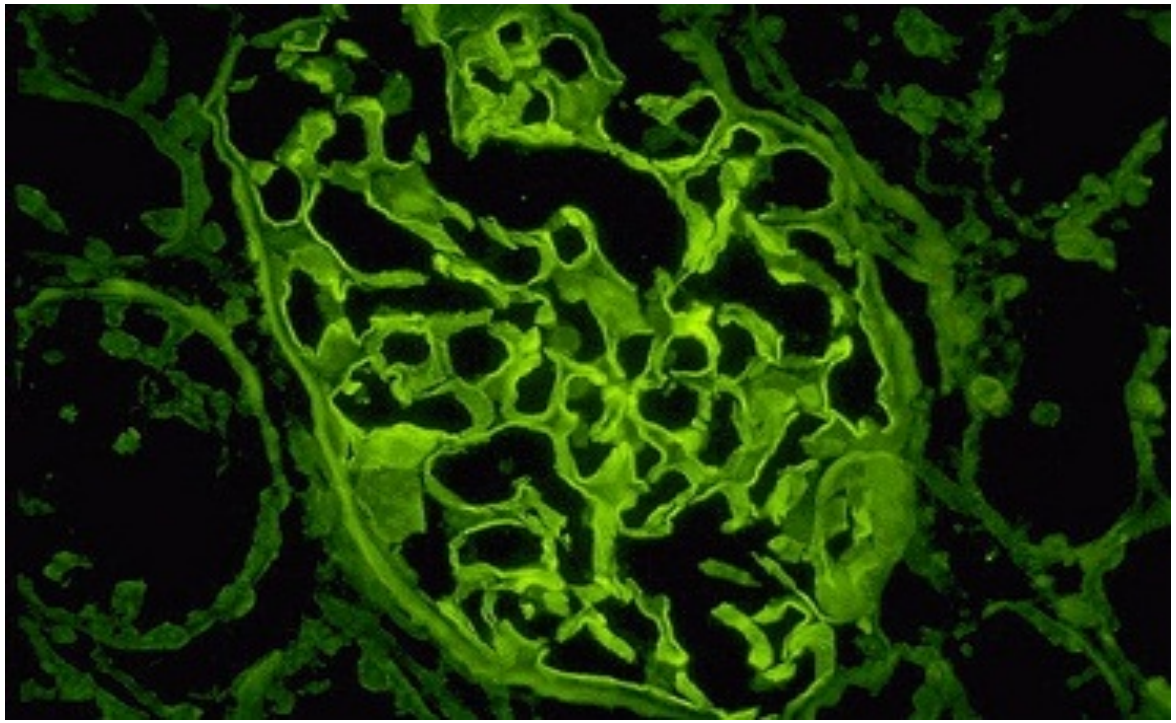


Iron stain in sputum





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



- 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

2.Idiopathic Pulmonary Hemosiderosis

- similar to those of Goodpasture syndrome but

a. No associated renal disease

b. No circulating anti-basement membrane antibody.

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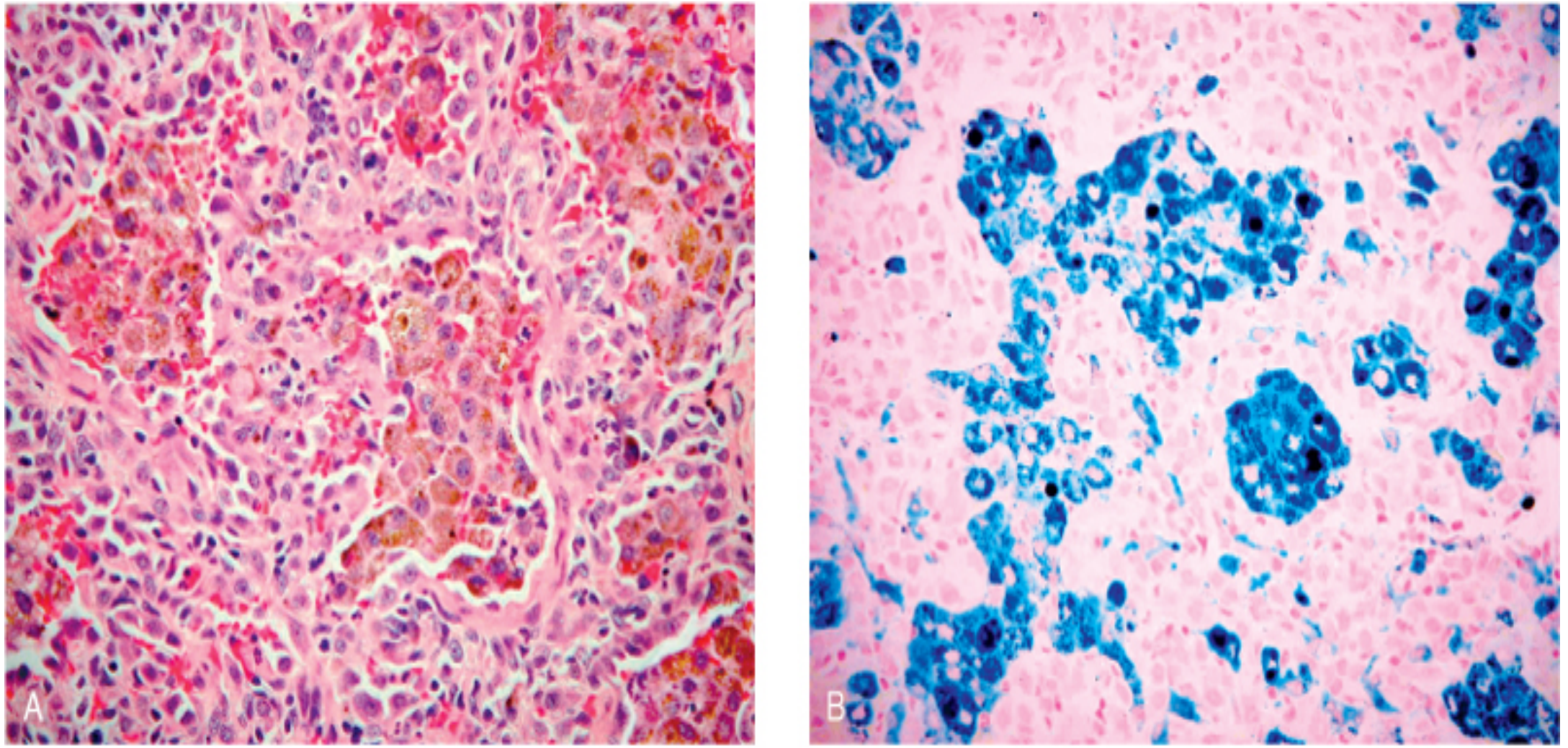
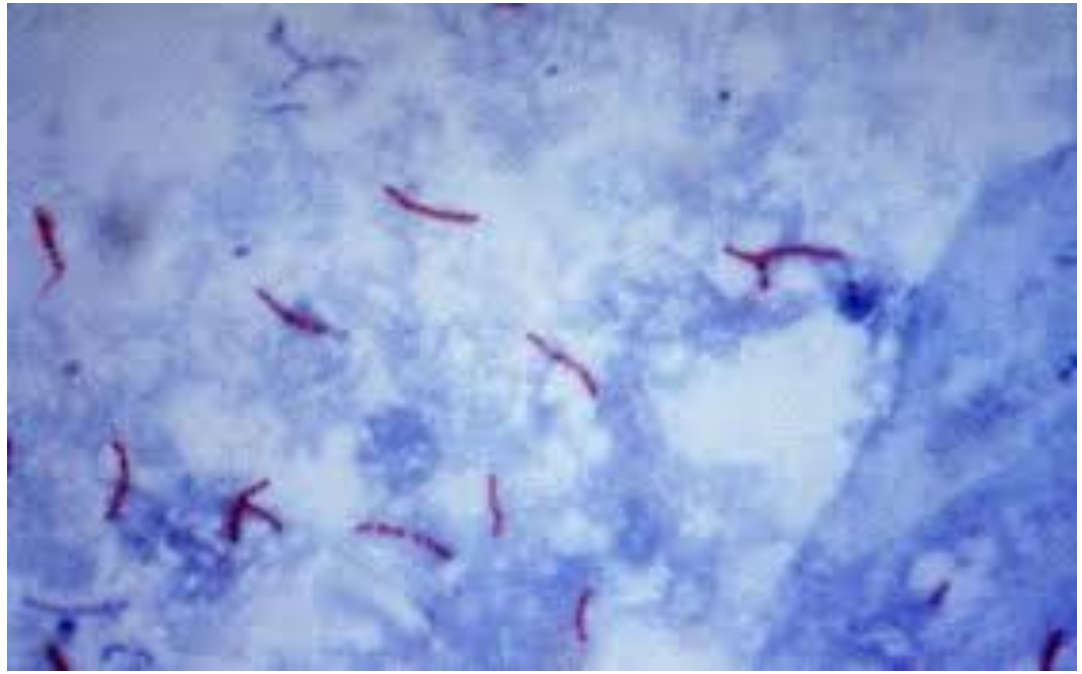
- Most cases occur in children, although the disease is reported in adults as well, who have a better prognosis
- With steroid and immunosuppressive therapy, survival has markedly improved from the historical 2.5 years;
- thus, an immune-mediated etiology is postulated

Diffuse alveolar hemorrhage syndrome –perl'sstain



Tuberculosis



- Tuberculosis is a communicable chronic disease

Epidemiology

- It flourishes under conditions of poverty, crowding, in old people and disease states such as

a. Diabetes mellitus,

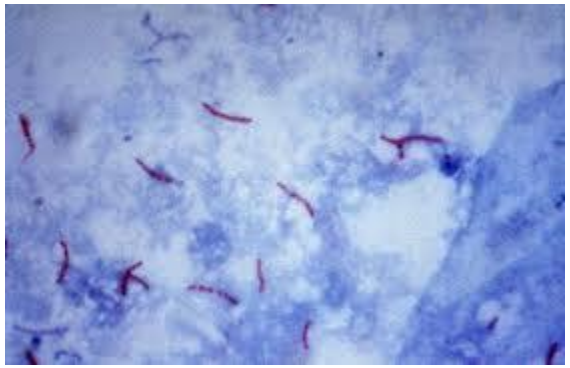
b. Hodgkin lymphoma,

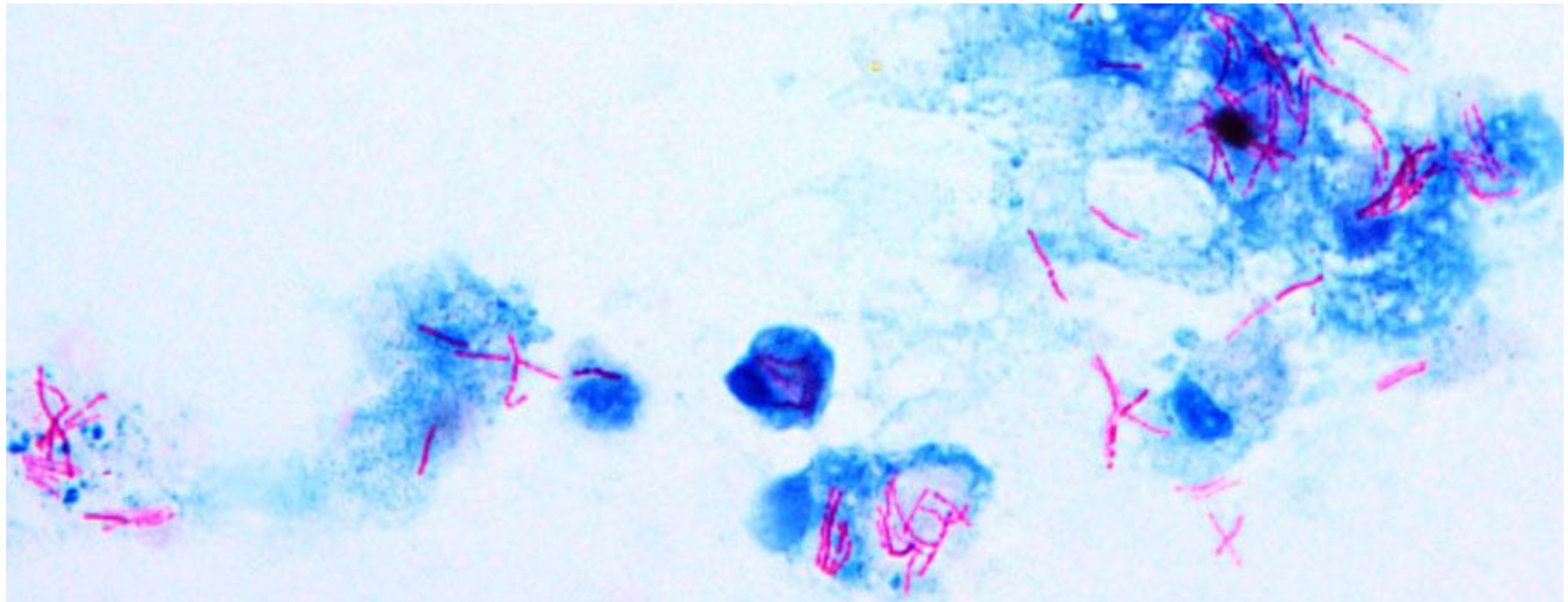
c. Silicosis

d. Immunosuppression.. Including AIDS..

Relationship of HIV and Tuberculosis

Etiology: mycobacterium tuberculosis which are acid fast bacilli





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

II. 3 weeks after exposure

- Development of cell-mediated immunity

a. 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 macrophages

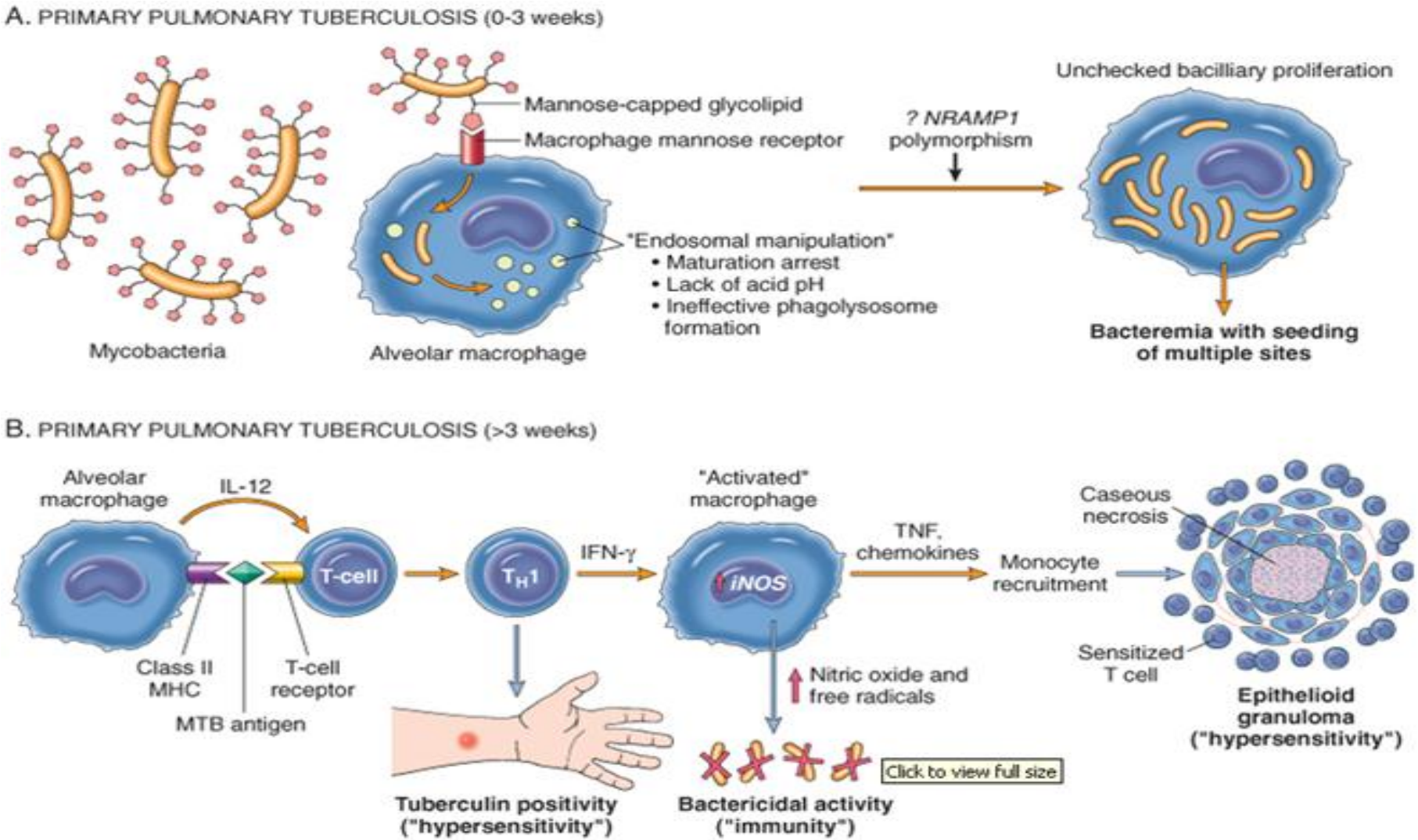
b. Activated macrophages release a variety of mediators

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

pathogenesis



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).

- Infection with M. tuberculosis typically leads to the development of delayed hypersensitivity, which can be detected by the tuberculin (Mantoux) test

Tuberculin test test

About 2 to 4 weeks after the infection has begun, intracutaneous injection of 0.1 mL of PPD induces a visible and palpable induration (at least 5 mm in diameter) that peaks in 48 to 72 hours.

- 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)

a. Certain viral infections,

b. Sarcoidosis

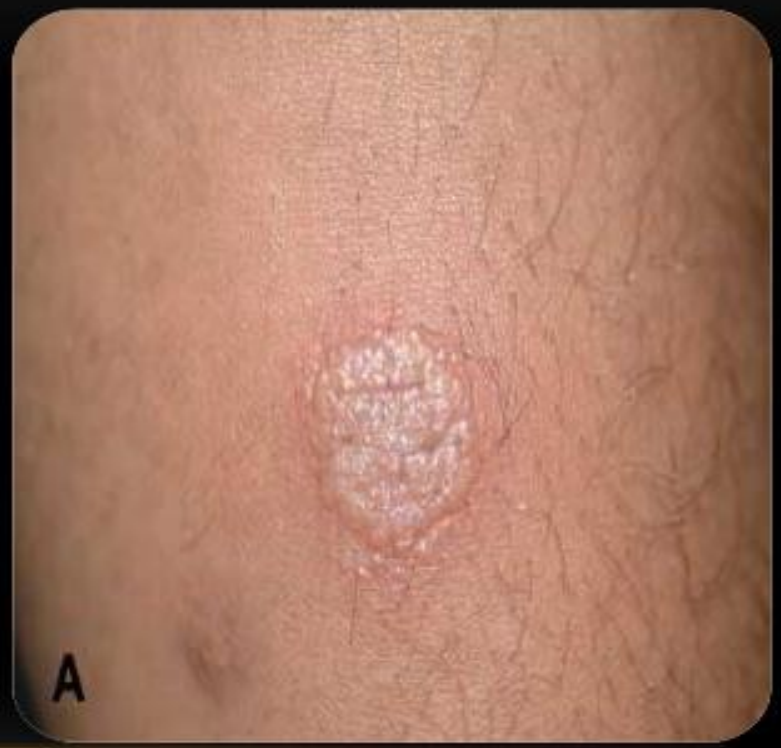
c. Immunosuppression

False-positive reactions

- May result from infection by atypical mycobacteria

READING THE TUBERCULIN SKIN TEST

- Read 2-3 days after placing the test
- Feel for induration
- Color change without induration is ***not*** included in the measurement
- Use a ruler or calipers
- Have someone else check if unsure
- Always document the exact size (mm) – not just “positive” or “negative”



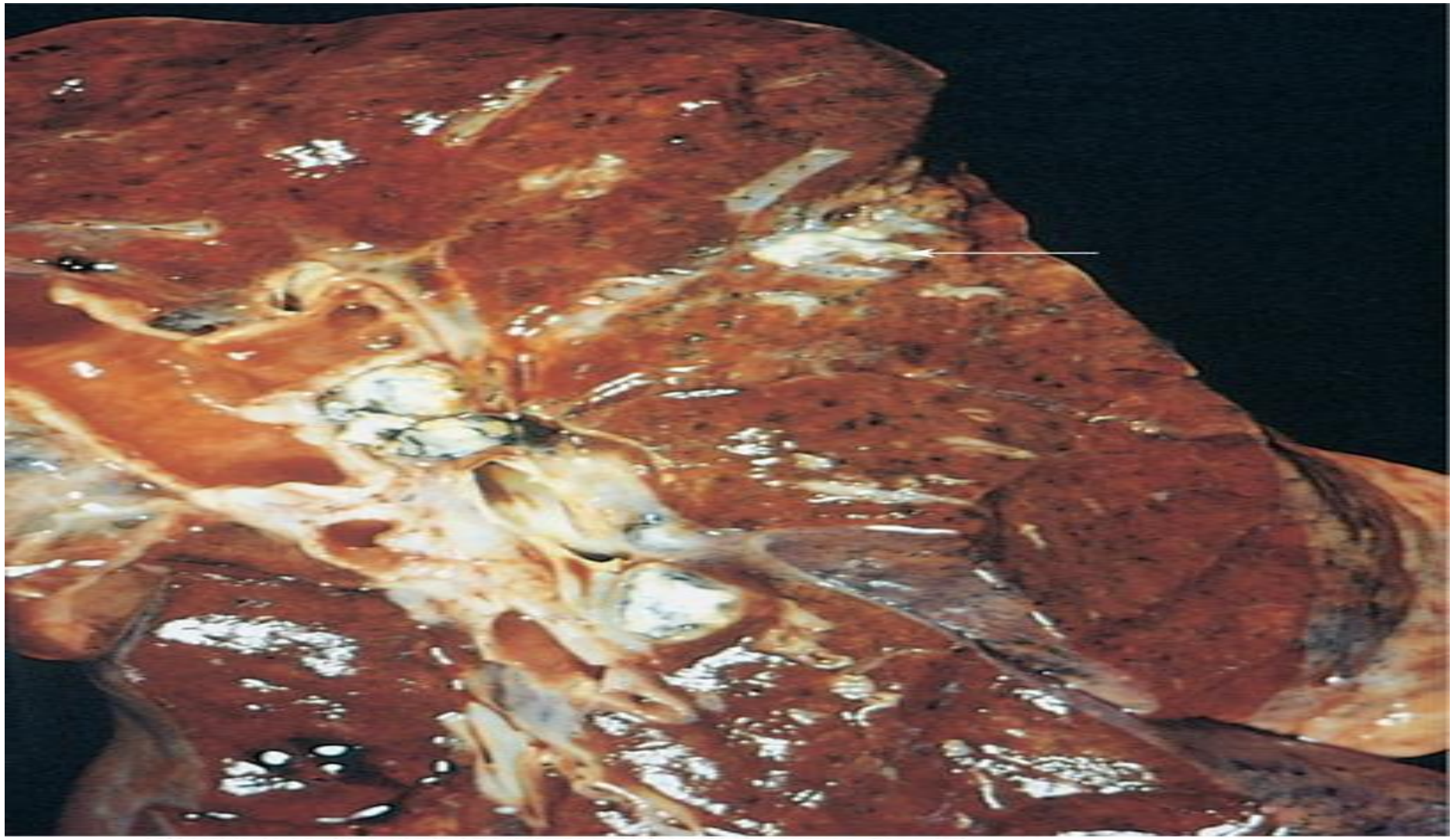
- About 80% of the population in certain Asian and African countries is tuberculin positive.
- About 3% to 4% of previously unexposed persons acquire active tuberculosis during the first year after "tuberculin conversion," and no more than 15% do so thereafter.
- **Thus, only a small fraction of those who contract an infection develop active disease**

- Primary TB: Is the form of disease that develops in previously unexposed and unsensitized patient.
- 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 granulomas

Primary TB

- Granulomas in the primary lung site: Ghon focus
- Ghon focus and granulomas in draining lymph nodes = Ghon complexaes

Primary Tuberculosis



- The Ghon complex undergoes progressive fibrosis, followed by radiologically detectable calcification (Ranke 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.

3) uncommonly, it may lead to progressive primary tuberculosis and this complication occurs in patients who are immunocompromised or in

- Secondary TB: Is the pattern of disease that arises in a previously sensitized host.

a. It may follow shortly after primary tuberculosis,

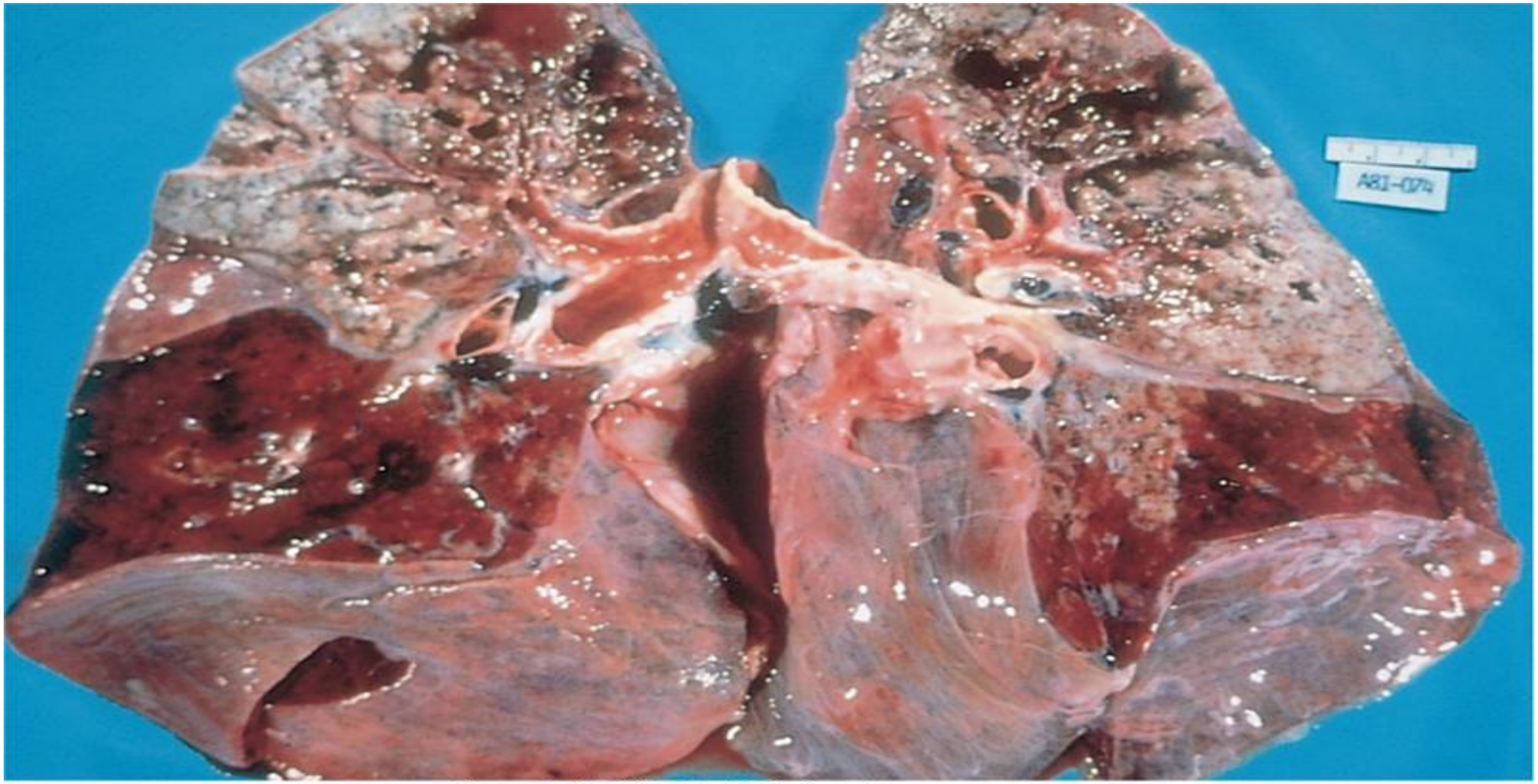
b. More commonly arises from reactivation of dormant primary TB decades after initial infection, particularly when host resistance is weakened.

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.

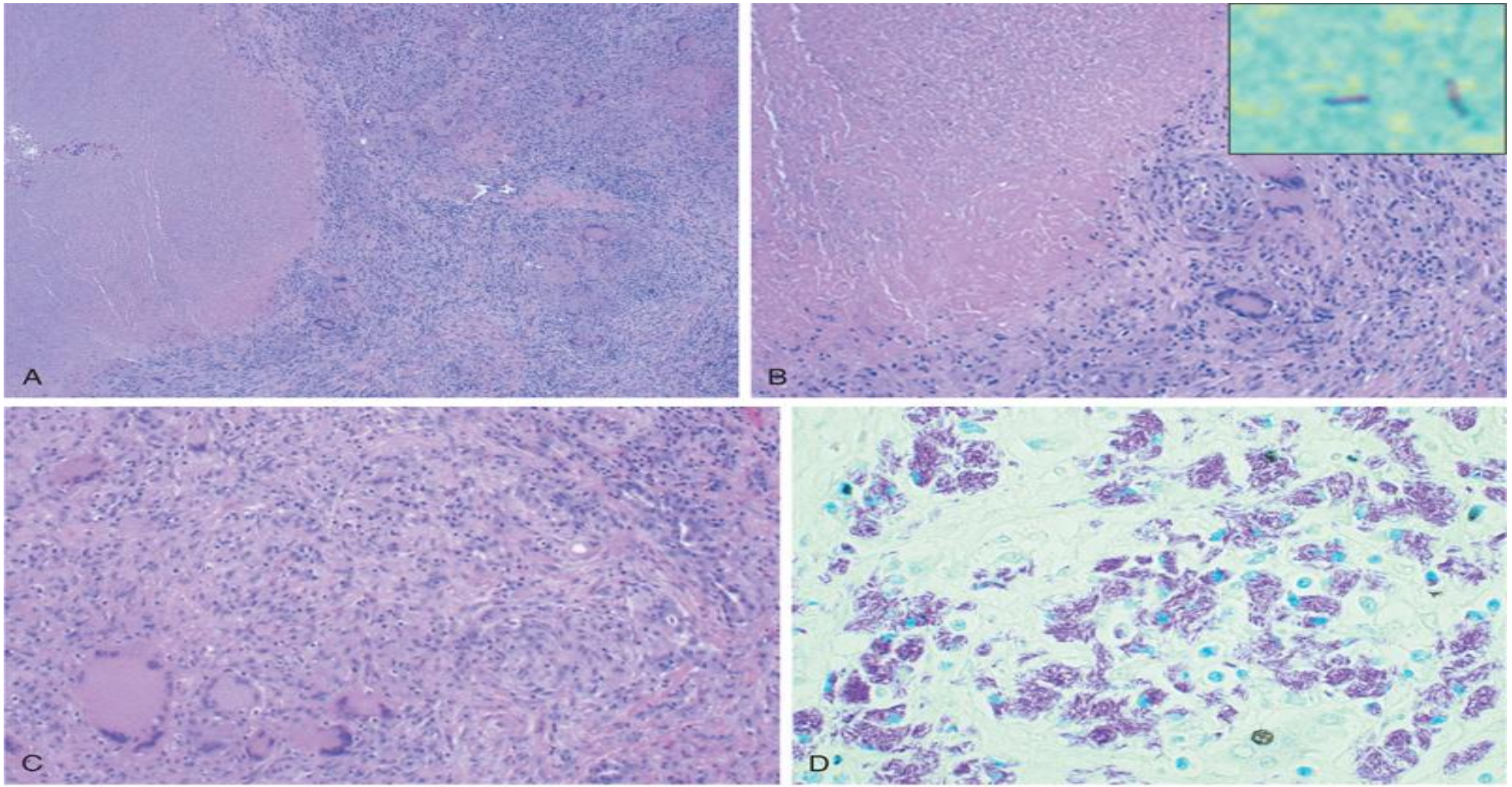
- Because of the preexistence of hypersensitivity, the bacilli excite marked tissue response to wall off the focus .
- As a result of this localization, the regional lymph nodes are less prominently involved early in the disease than they are in primary tuberculosis
- Cavitation occurs in the secondary form, leading to erosion into and dissemination along airways.

Secondary tuberculosis

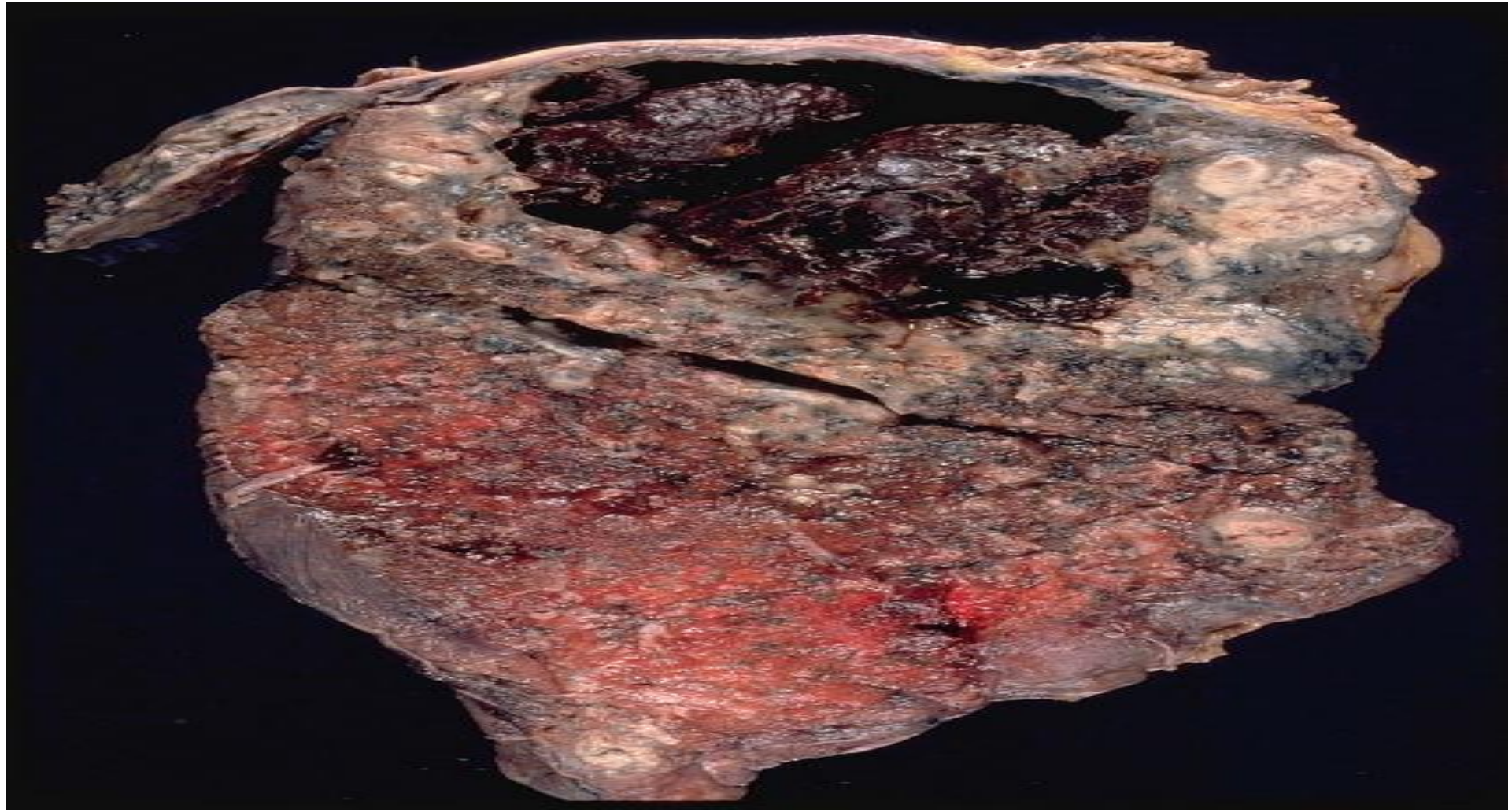


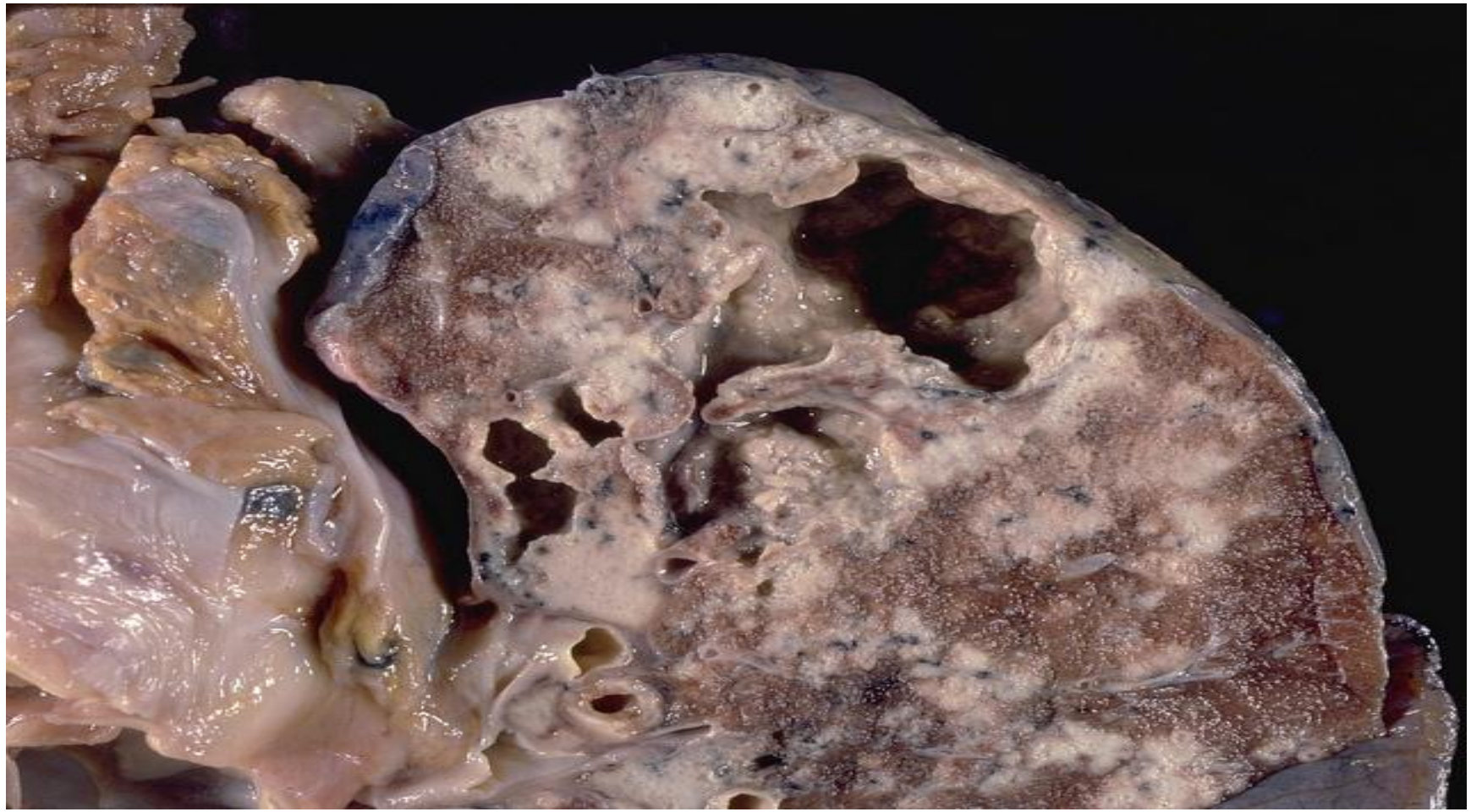
Kumar et al: Robbins Basic Pathology, 9e.

Tuberculosis



CAVITATION





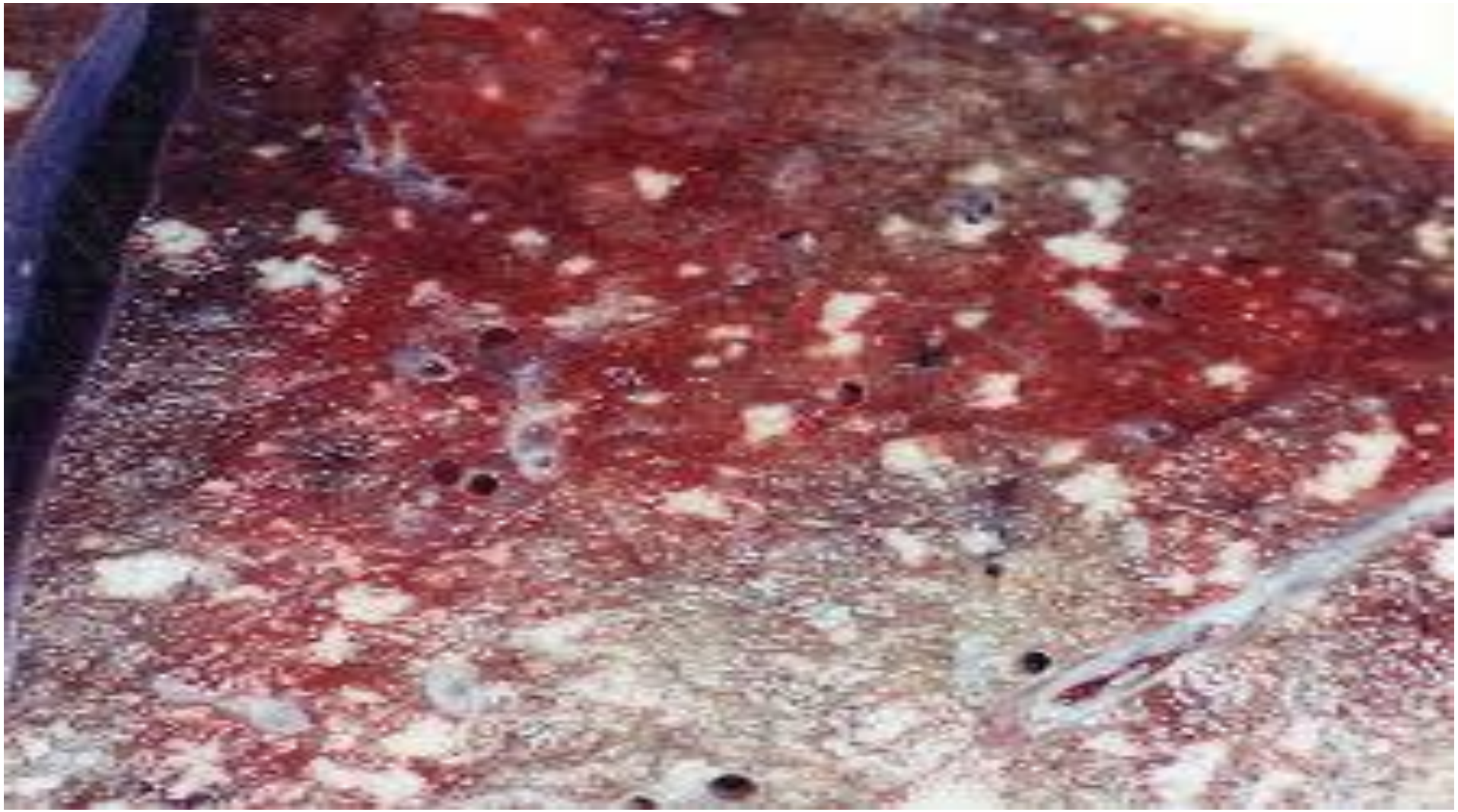
Morphology of secondary TB

- 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

1. Miliary pulmonary disease

- 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
- Individual lesions are small, (2 mm) foci scattered through the lung parenchyma

Pulmonary MILIARY TB



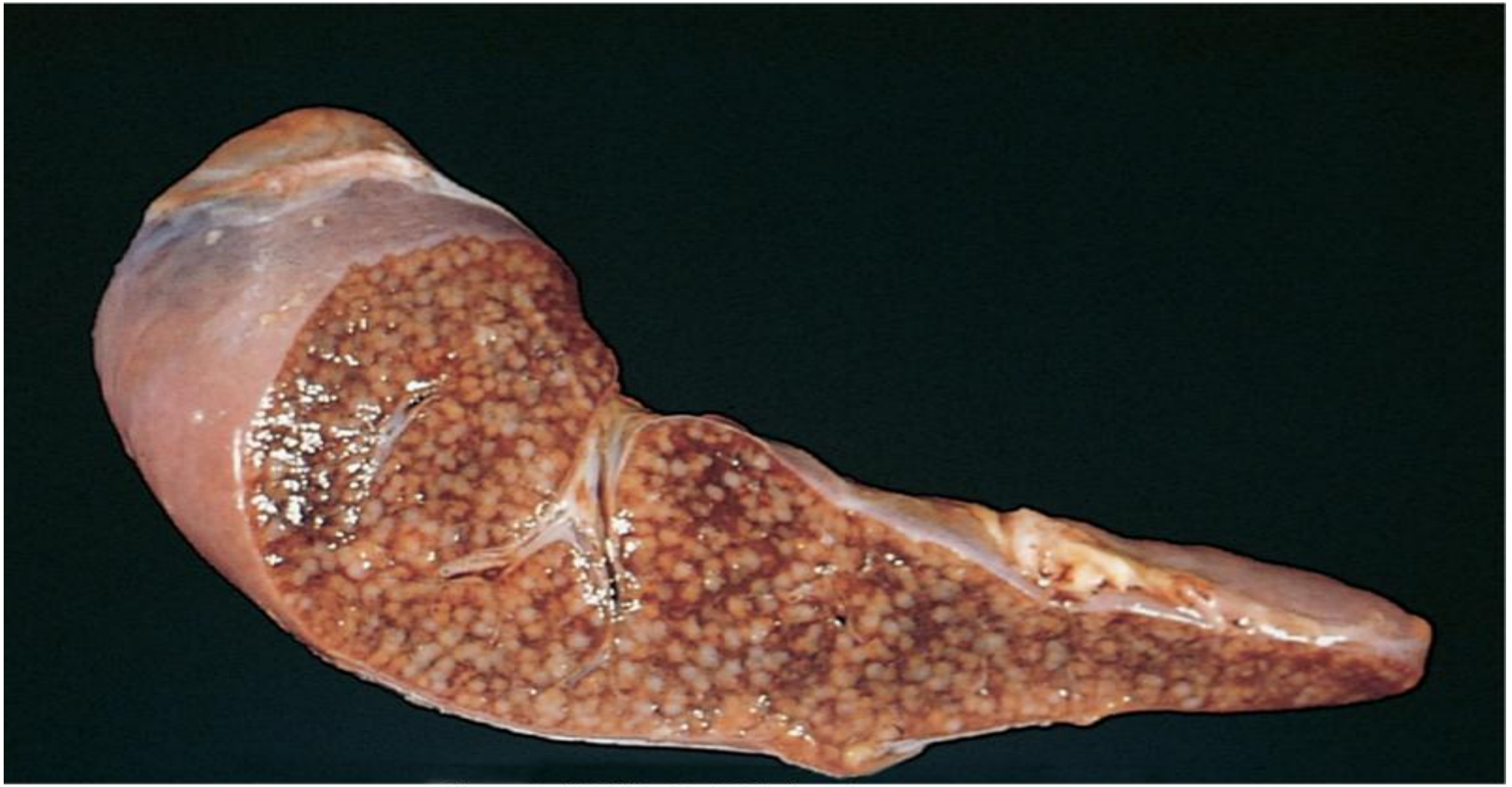
2. Systemic miliary tuberculosis

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

3. Isolated-organ tuberculosis

- Tuberculous involvement of Vertebrae is called (Pott disease).

Miliary TB in spleen



Clinical Features

- 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

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Extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved for example,:

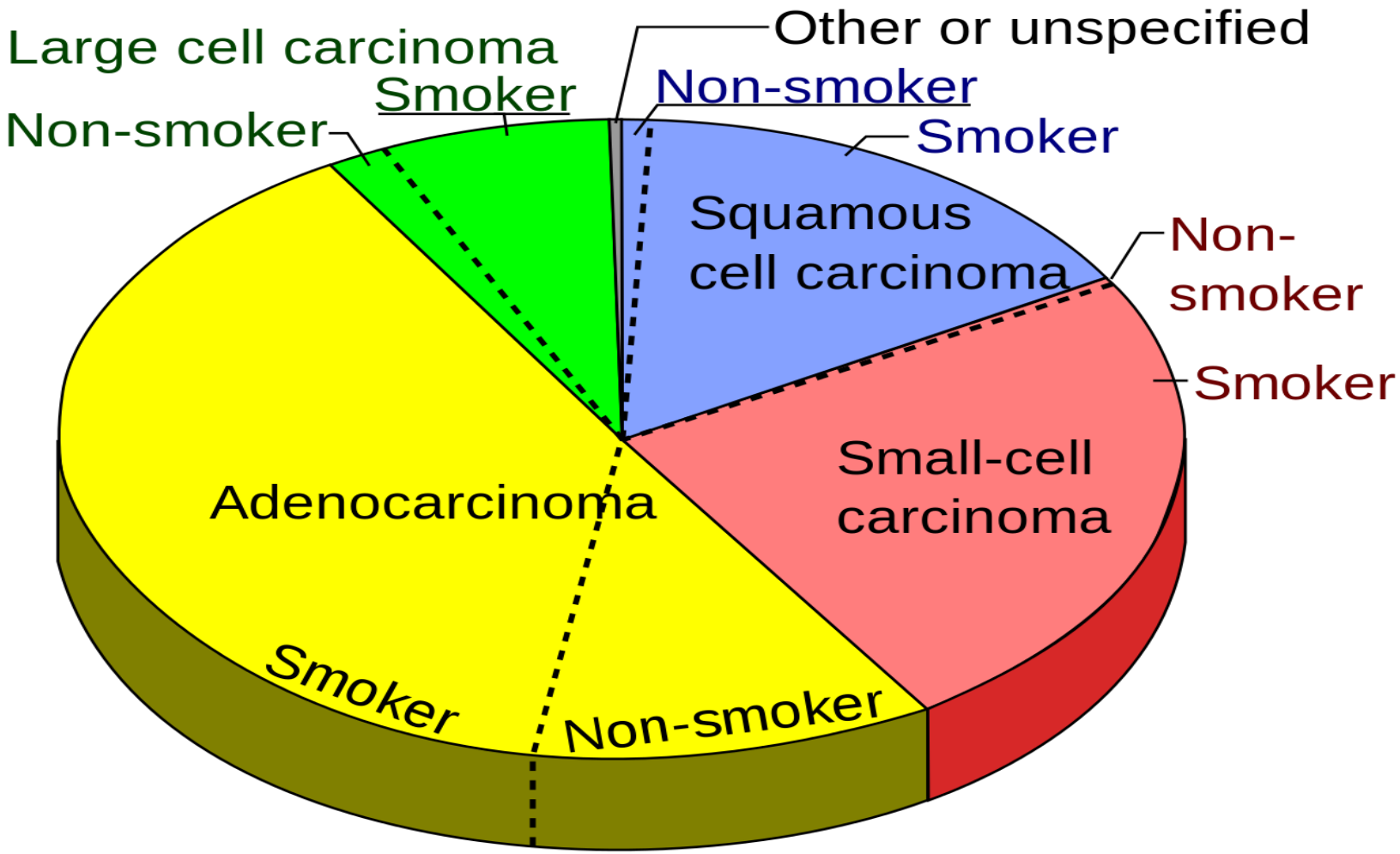
a. Tuberculous salpingitis may present as infertility,

b.Tuberculous meningitis with headache and neurologic deficits,

c. Pott disease with back pain and paraplegia

Lung carcinoma

Lung tumors


Large cell carcinoma
Non-smoker
Smoker
Other or unspecified
Non-smoker
Smoker
Squamous cell carcinoma
Non-smoker
Smoker
Small-cell carcinoma
Adenocarcinoma
Smoker
Non-smoker

- 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

a. Adenocarcinoma

b. Squamouscell carcinoma,

c. Small cell carcinoma,

d. Large cell carcinoma

- 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 subtypes

- 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

- 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.

1. 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

2. 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

4. ALK tyrosine kinase fusion genes and c-

- These abnormalities, 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

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

- MORPHOLOGY

1. Squamous cell carcinomas :

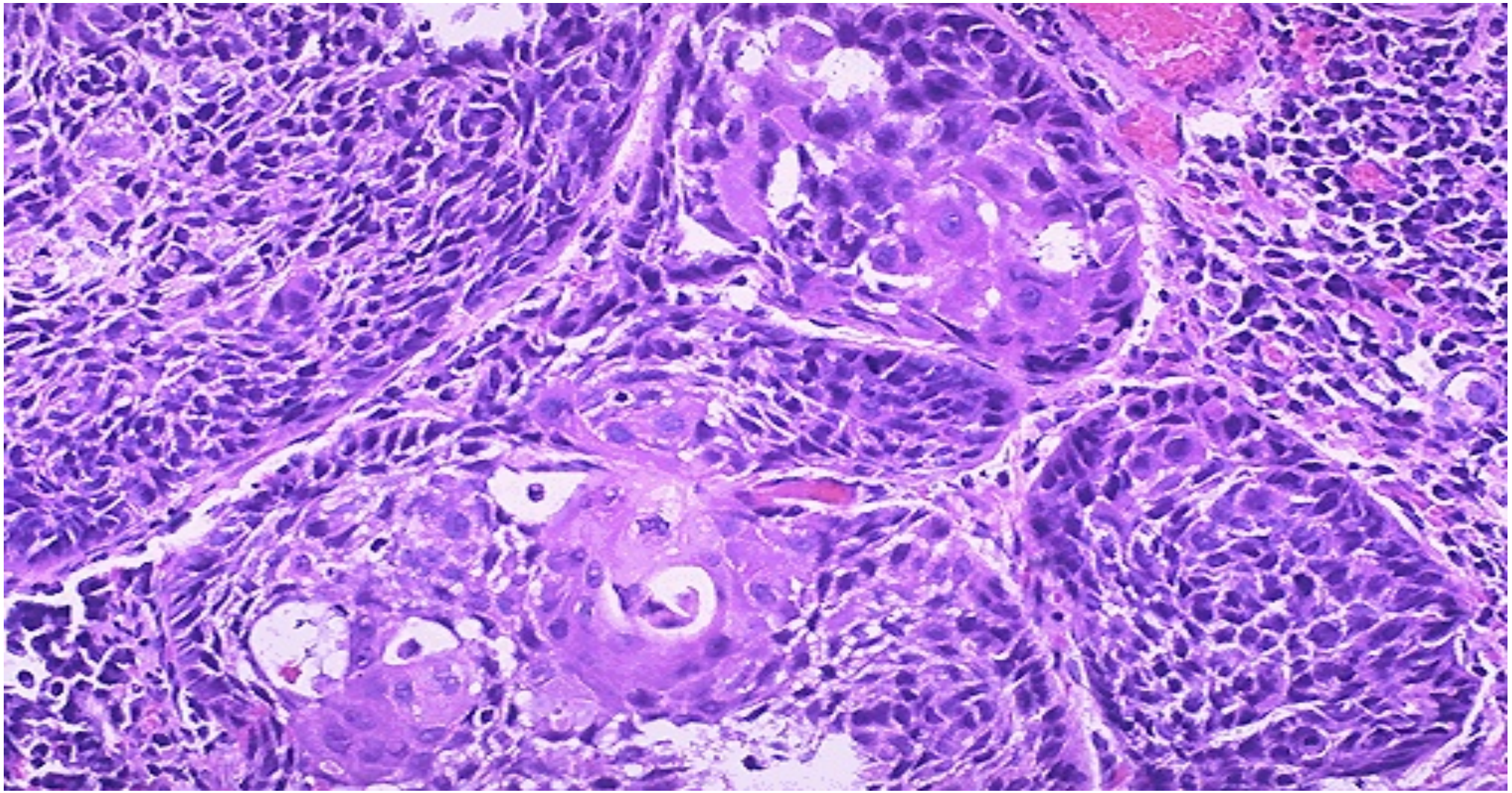
a. Are more common in men than in women

b. Are closely correlated with a smoking history;

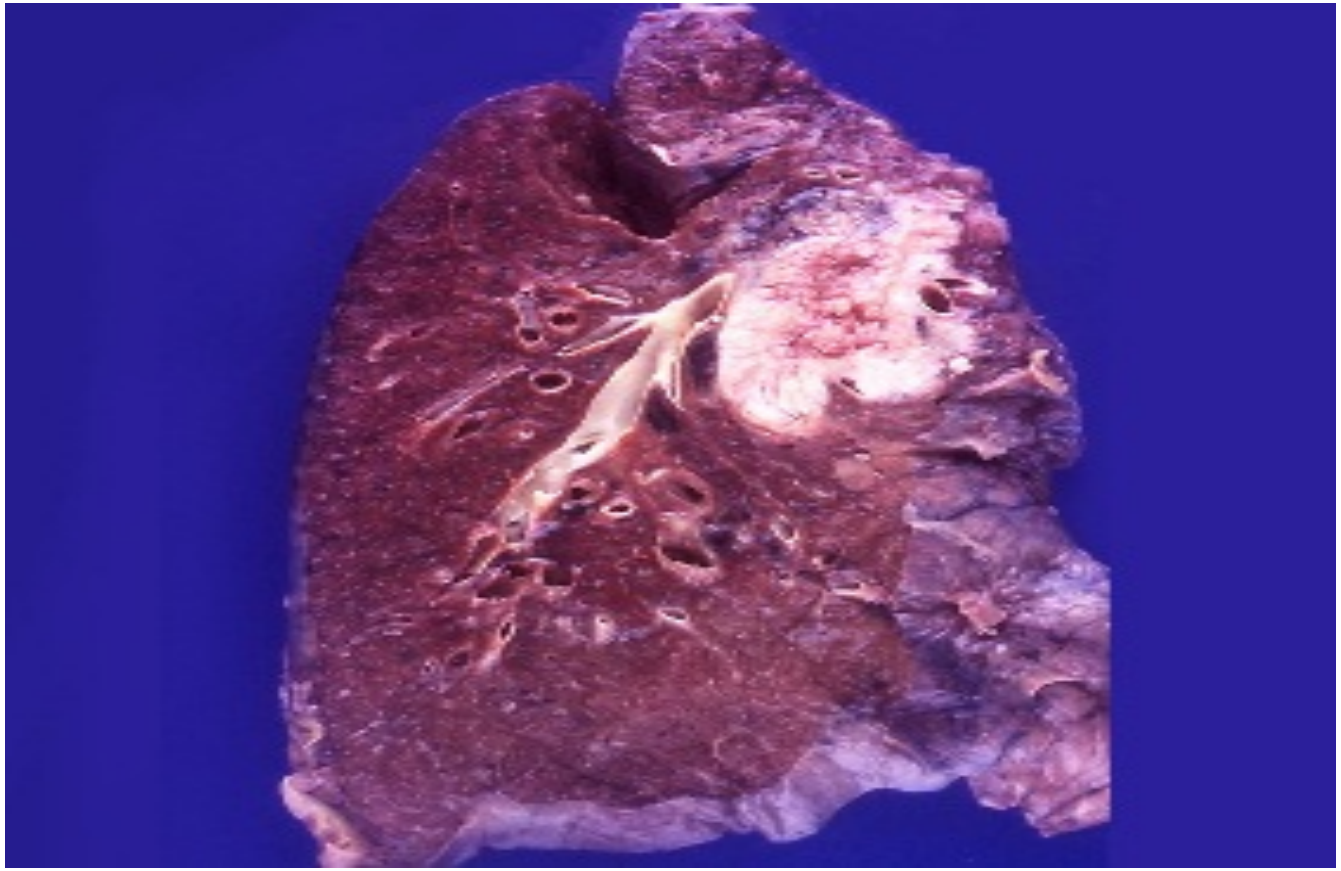
c. They tend to arise centrally in major bronchi and eventually spread to local hilar nodes,

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

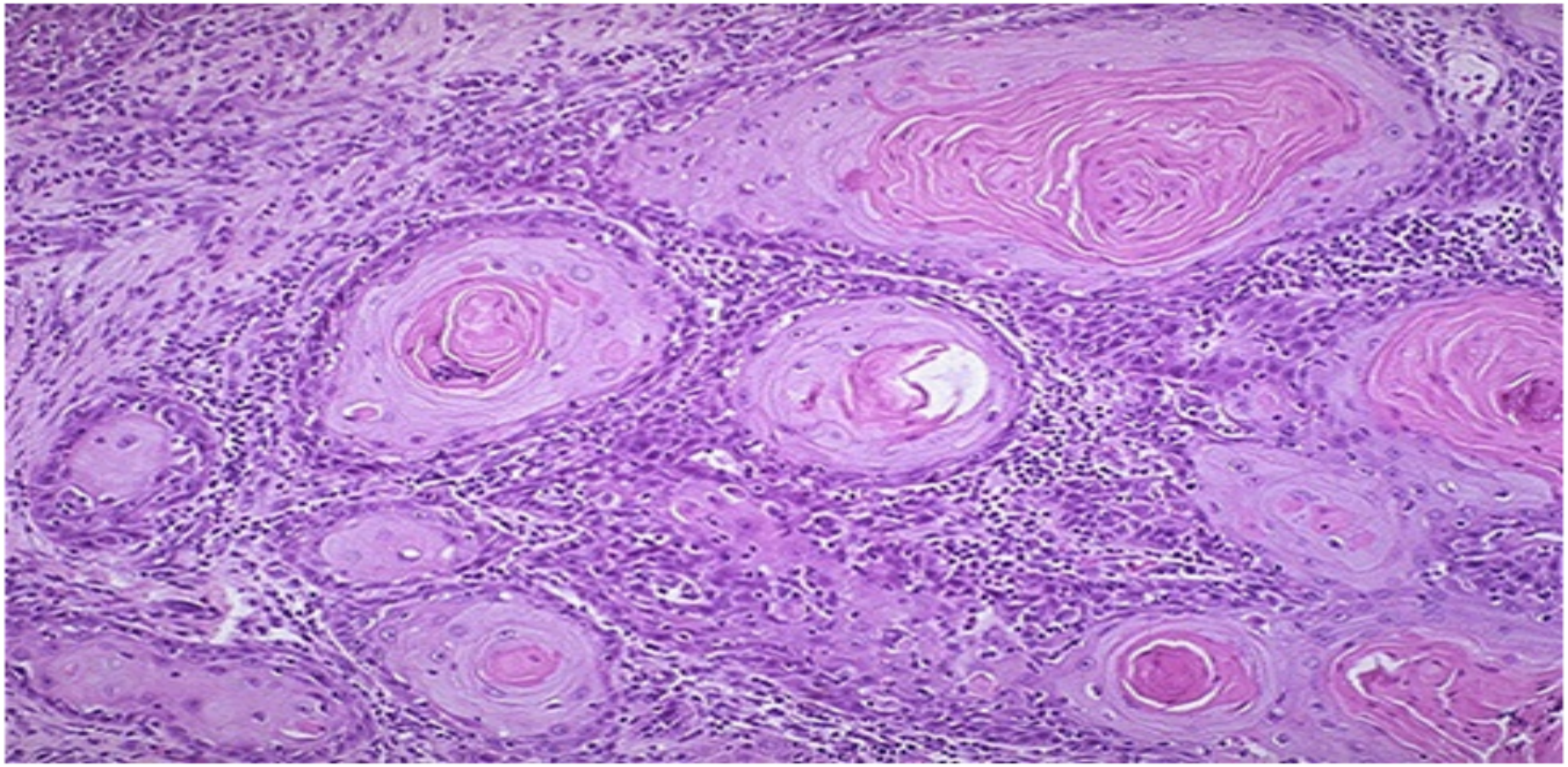
Squamous cell carcinoma of lung



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

- 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).

3. Small cell lung carcinomas (SCLCs) are:

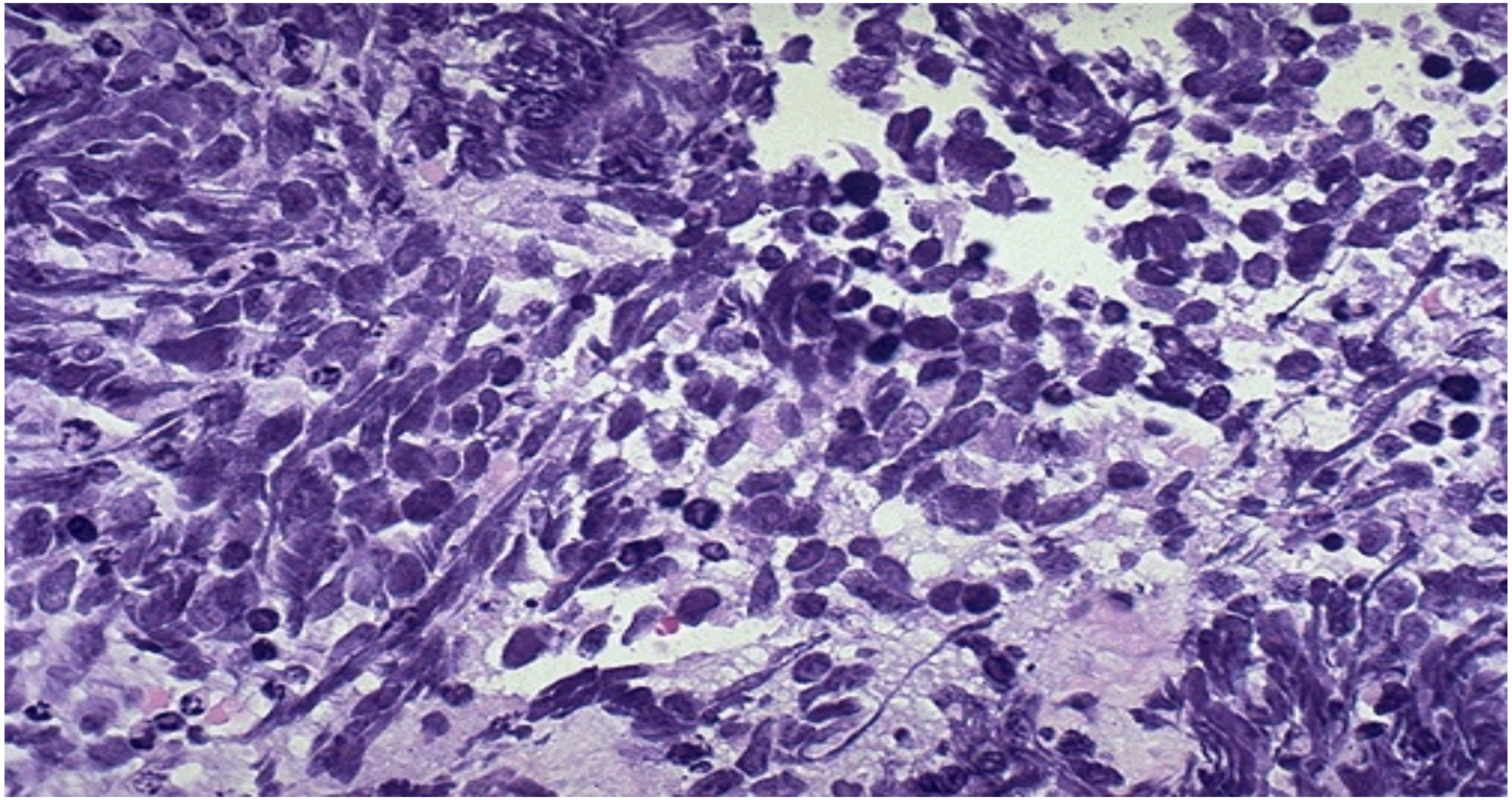
a. Centrally located with extension into the lung parenchyma

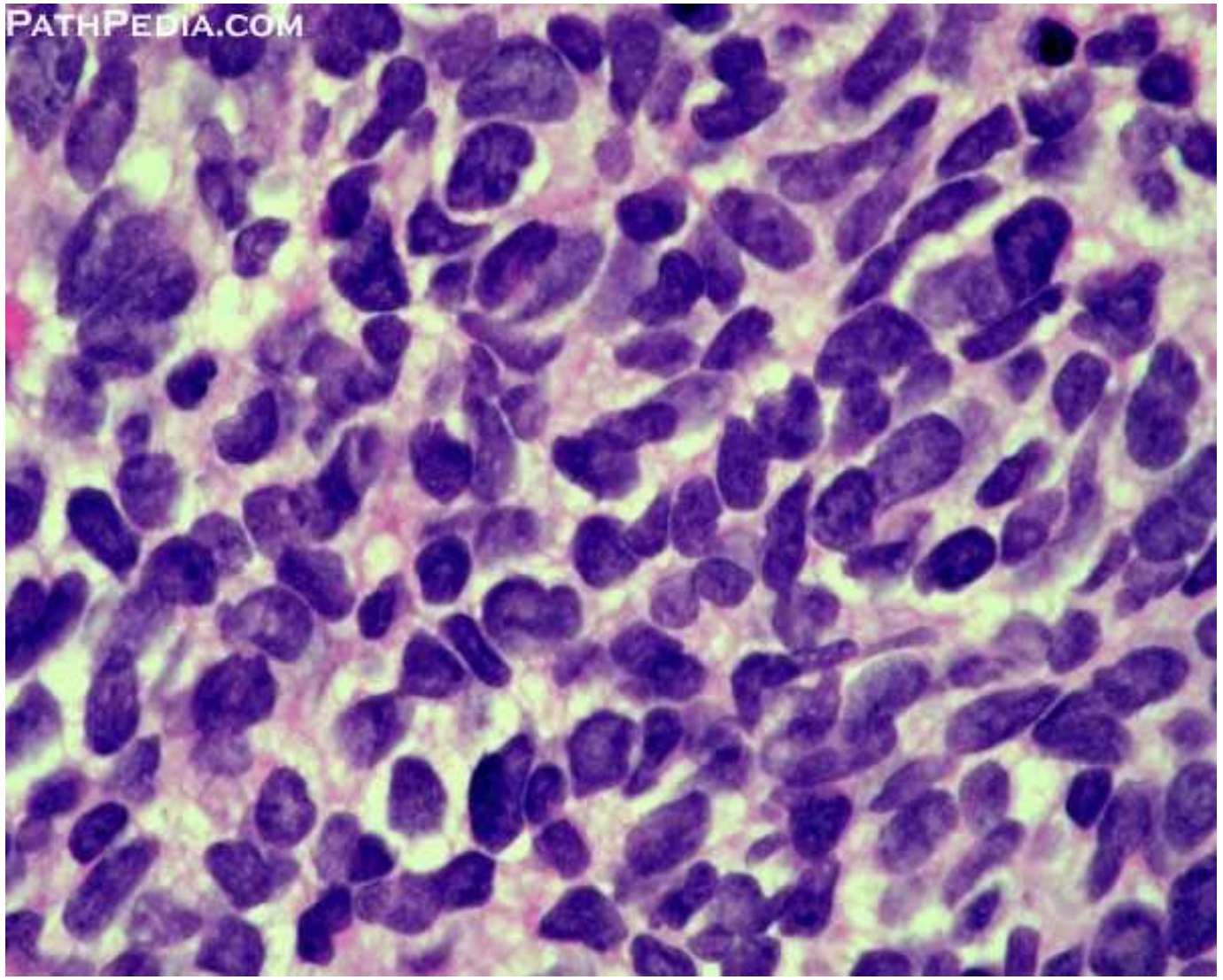
b. Early involvement of the hilar and mediastinal nodes.

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

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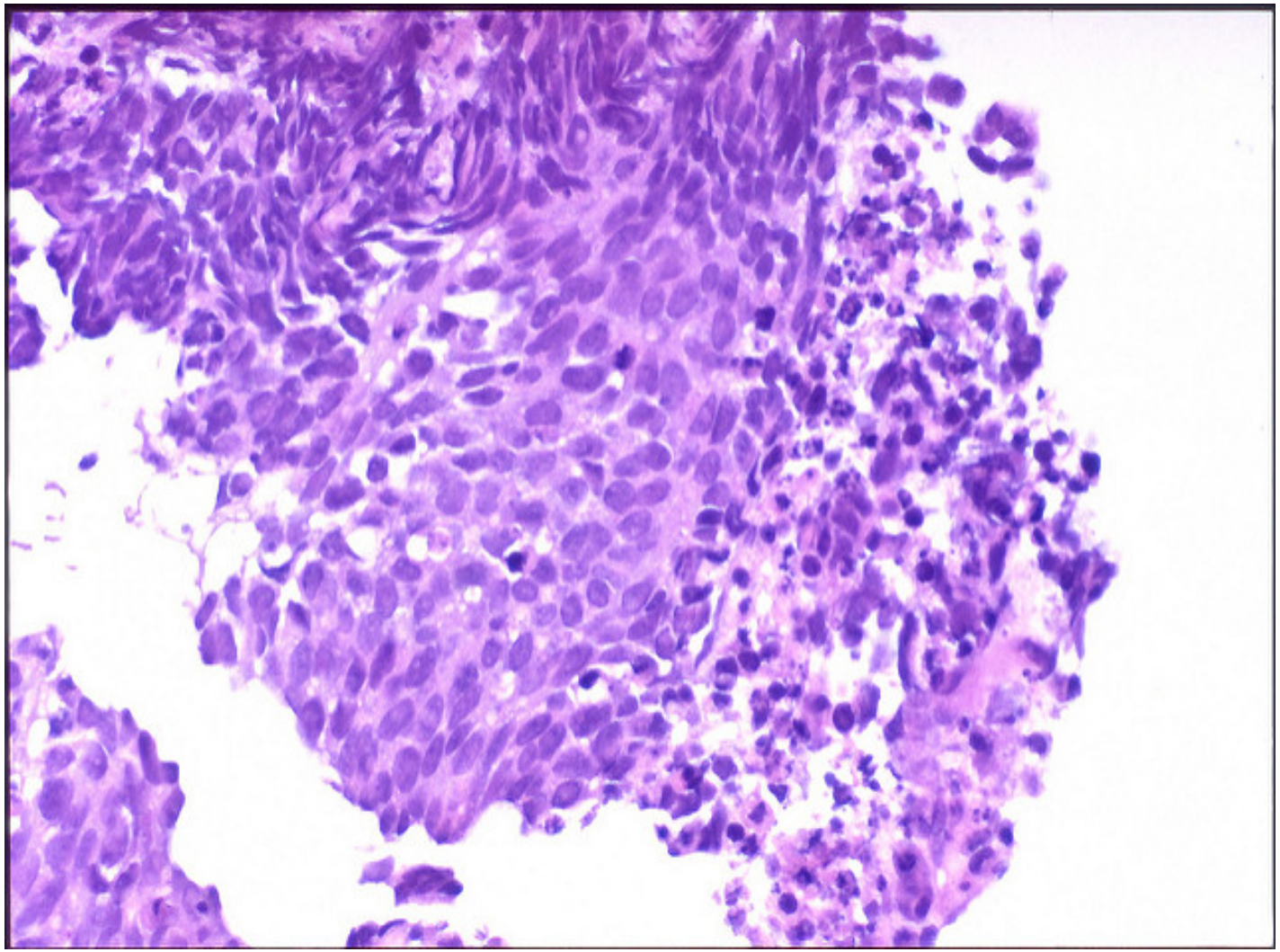
Crushing artefacts in small cell carcinoma



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 lung cancer develop clinically overt paraneoplasticsyndromes.

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


THANK YOU!