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..

NOTE:

- In areas of the world where HIV infection is prevalent, it has become the single most important risk factor for the development of tuberculosis

Etiology

1- M. tuberculosis hominis is responsible for most cases of tuberculosis

- The reservoir of infection typically is found in persons with active pulmonary disease
- Most infections are acquired by direct person to person transmission of airborne droplets of organisms from an active case to a susceptible host

2. Mycobacterium bovis

- Causes intestinal tuberculosis
- Is contracted by drinking milk contaminated with the microorganism
- Infection is now rare in developed nations, but it is still seen in countries with tuberculous dairy cows and sales of unpasteurized milk.

- In years past, intestinal tuberculosis contracted by the drinking of contaminated milk was a common primary focus of tuberculosis.
- In developed countries today, intestinal tuberculosis is more often a complication of advanced pulmonary secondary tuberculosis, resulting from swallowing of coughed up infective material.

- The organisms are trapped in mucosal lymphoid aggregates of the small and large bowel, which then undergo inflammatory enlargement with ulceration of the overlying mucosa, particularly in the ileum

PATHOGENESIS

- The pathogenesis in the previously unexposed immunocompetent person is centered on the development of a targeted cell mediated immunity that confers resistance to the organism and results in development of tissue hypersensitivity to tubercular antigens.
- The sequence of events from inhalation of the infectious inoculum

I. In the first 3 weeks:

- 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

- Despite the bacteremia, most persons at this stage are symptomatic or have a mild flu-like illness.
- The genetic makeup of the patient may influence the course of the disease
- People with polymorphisms of the NRAMP1 (natural resistance associated macrophage protein 1) gene, the disease may progress from this point without development of an effective immune response

- NRAMP1 is a transmembrane ion transport protein found in endosomes and believed to contribute to microbial killing

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 generates

TH1 subtype of CD4+ T cells that secret Gamma- IFN which activates macrophages

b. Activated macrophages release a variety of mediators and upregulate expression of genes with important downstream effects, including

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

a. Signifies cell-mediated hypersensitivity to tubercular antigens

b. It does not differentiate between infection and disease

- False-negative reactions (or skin test anergy)

a. Certain viral infections,

b. Sarcoidosis

c. Immunosuppression

False-positive reactions

- May result from infection by atypical mycobacteria

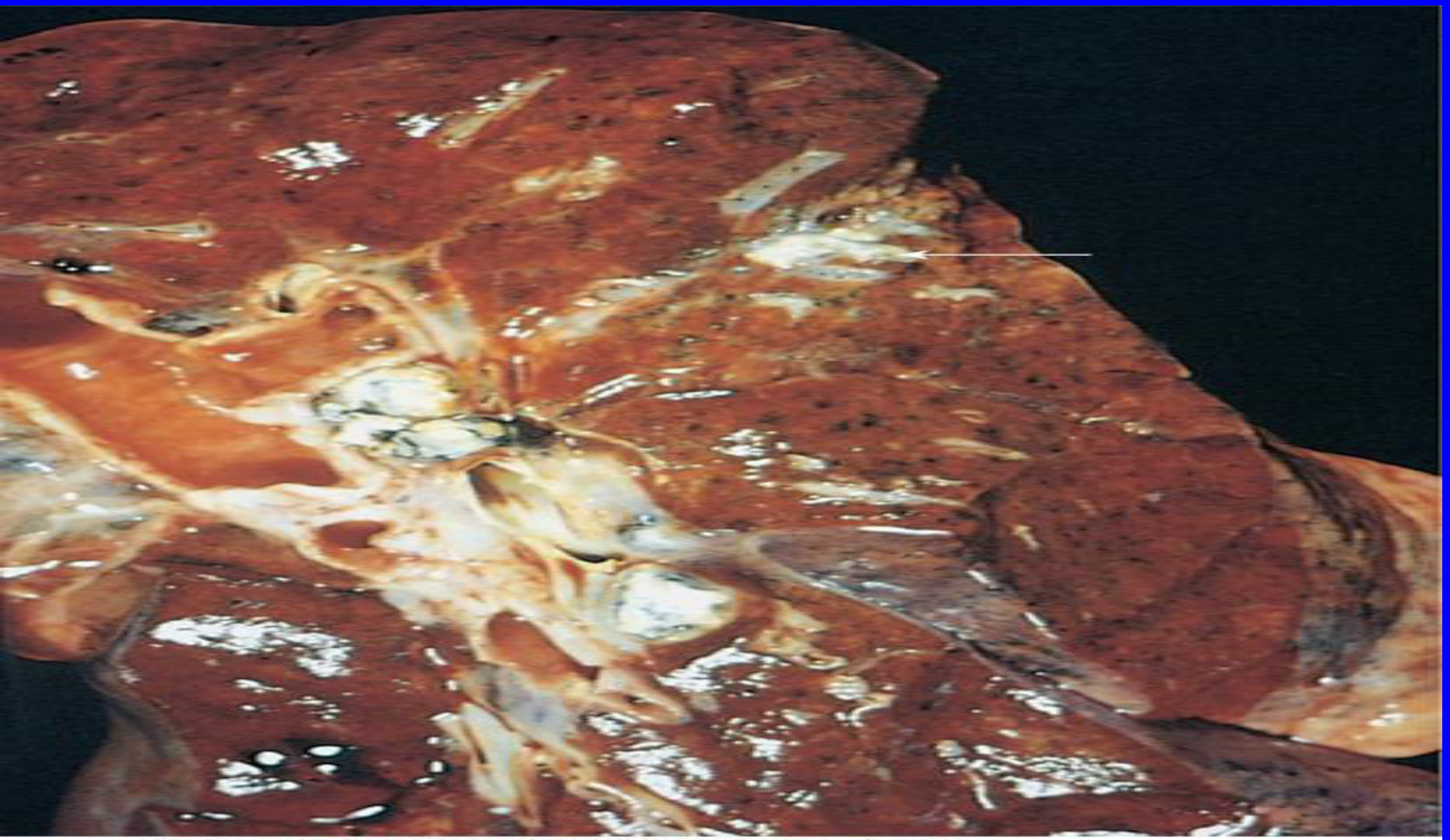
- About 80% of the population in certain Asian and African countries is tuberculin positive.
- About 3% to 4% of previously unexposed persons acquire active tuberculosis during the first year after "tuberculin conversion," and no more than 15% do so thereafter.
- **Thus, only a small fraction of those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

Primary Tuberculosis

- 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

- Tubercle bacilli, travel in lymph drainage to the regional nodes, forming granuloma in the lymph nodes.
- The combination of Ghon focus and nodal involvement is called Ghon complex
- In approximately 95% of cases, development of cell-mediated immunity controls the infection

Primary Tuberculosis



Kumar et al: Robbins Basic Pathology, 9e.

- 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 malnourished children or in elderly persons

- The incidence of progressive primary tuberculosis is particularly high in HIV-positive patients with an advanced degree of immunosuppression (i.e., CD4+ counts below 200 cells/μL).

- Immunosuppression results in an inability to mount a CD4+ T cell-mediated immunologic reaction that would contain the primary focus
- Because hypersensitivity and resistance are most often concomitant factors, the lack of a tissue hypersensitivity reaction results in the absence of the characteristic caseating granulomas (nonreactive tuberculosis)

- Persons with primary tuberculosis are infected but do not have active disease and therefore cannot transmit organisms to others.
- When their immune defenses are lowered, the infection may reactivate to produce communicable and potentially life-threatening disease

Secondary Tuberculosis

- 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.

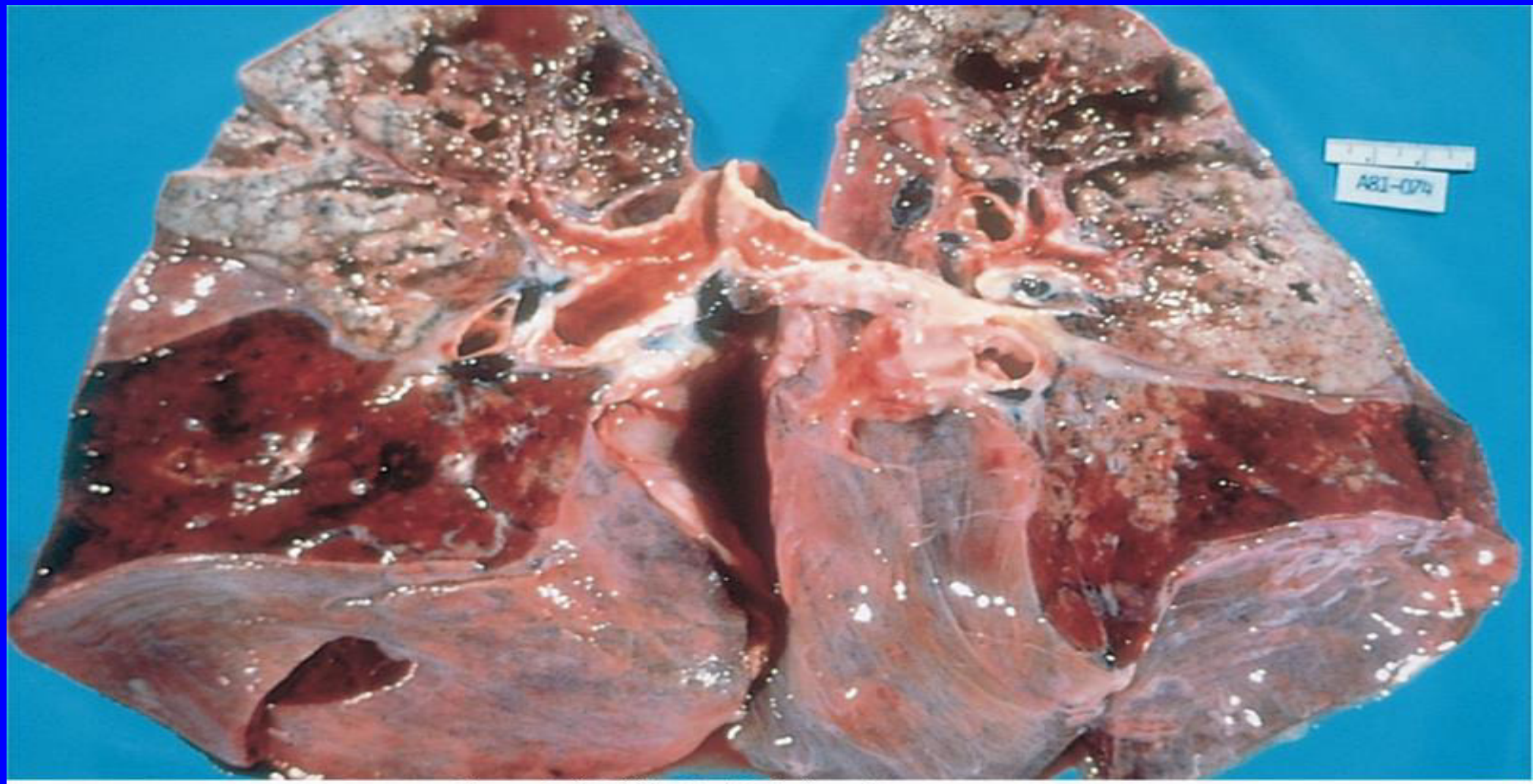
c. It also may result from exogenous reinfection because of waning of the protection afforded by the primary disease

- 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.

- Such changes become an important source of infectivity, because the patient now produces sputum containing bacilli.

Secondary tuberculosis



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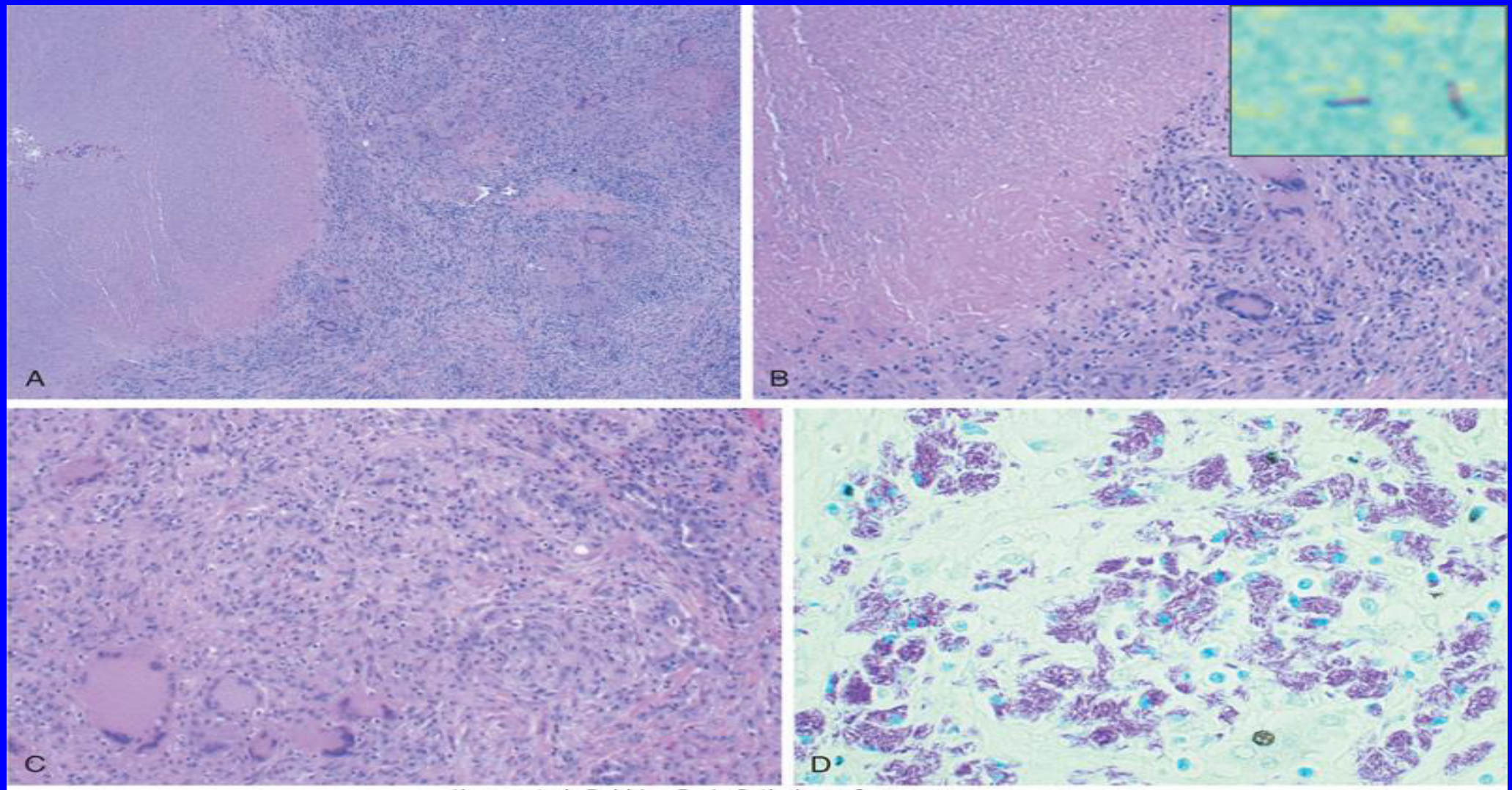
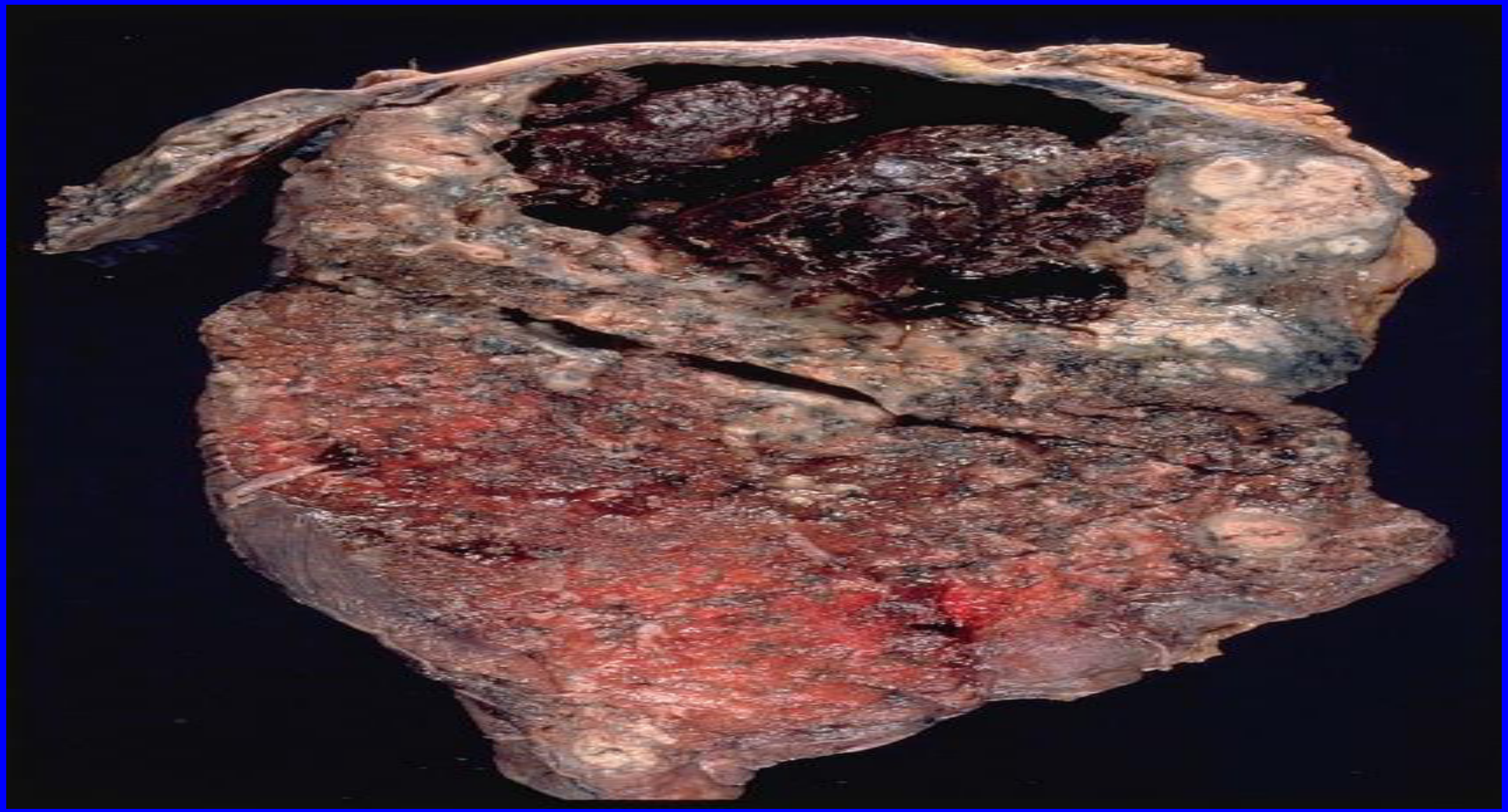
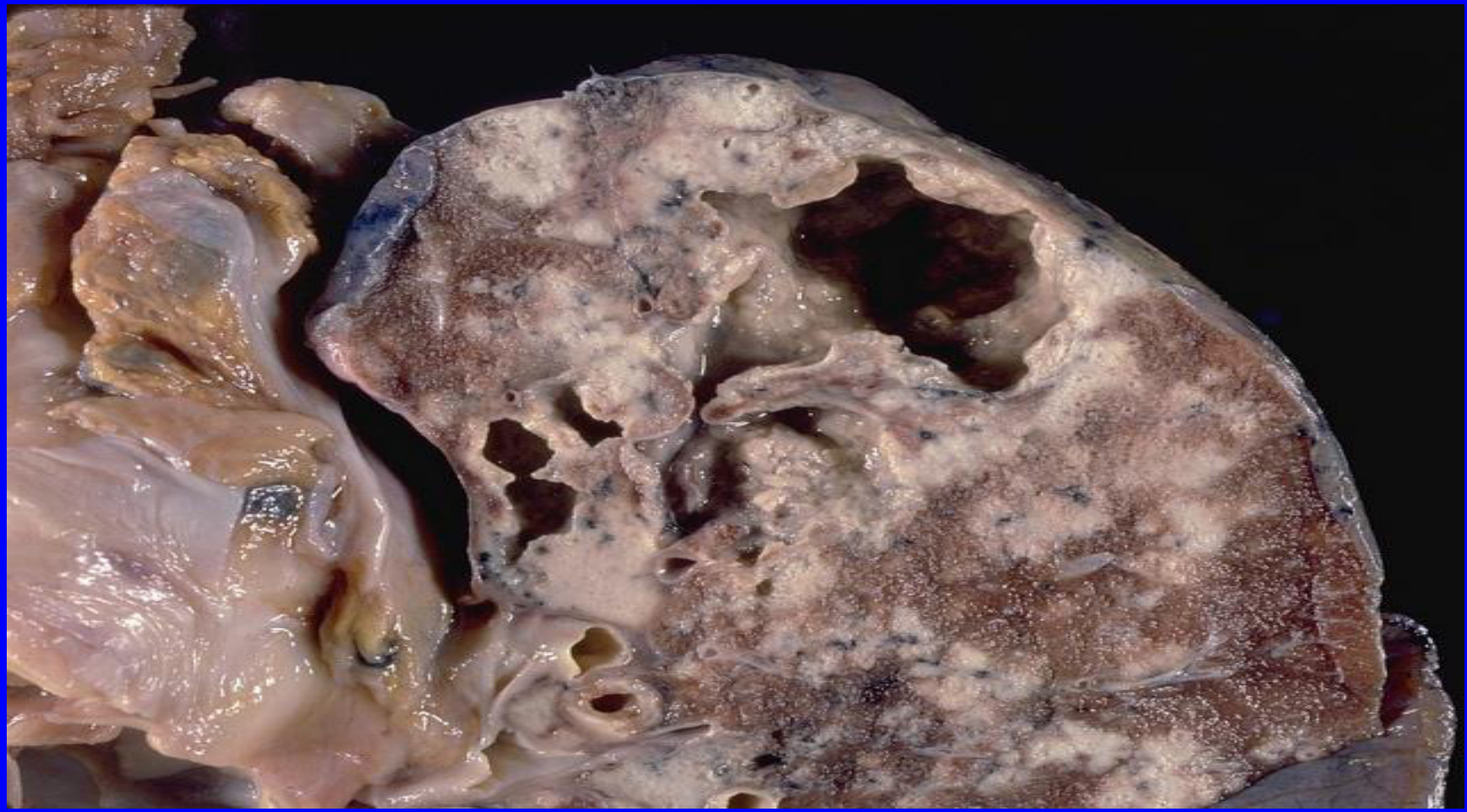
Tuberculosis



CAVITATION



CAVITATION AND CASEATION



- Secondary tuberculosis should always be an important consideration in HIV-positive patients who present with pulmonary disease
- Although an increased risk of tuberculosis exists at all stages of HIV disease, the manifestations differ depending on the degree of immunosuppression

1. Patients with CD4+ counts greater than 300 cells/mm present with "usual" secondary tuberculosis
2. Patients with CD4+ counts below 200 cells/mm present with a clinical picture that resembles progressive primary tuberculosis (lower and middle lobe consolidation, and, no granulomas, or cavitations (non-reactive disease).

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
- If the treatment is inadequate, or if host

, defences are impaired, the infection may spread by direct expansion by dissemination through lymphatic channels, or within the vascular system.

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

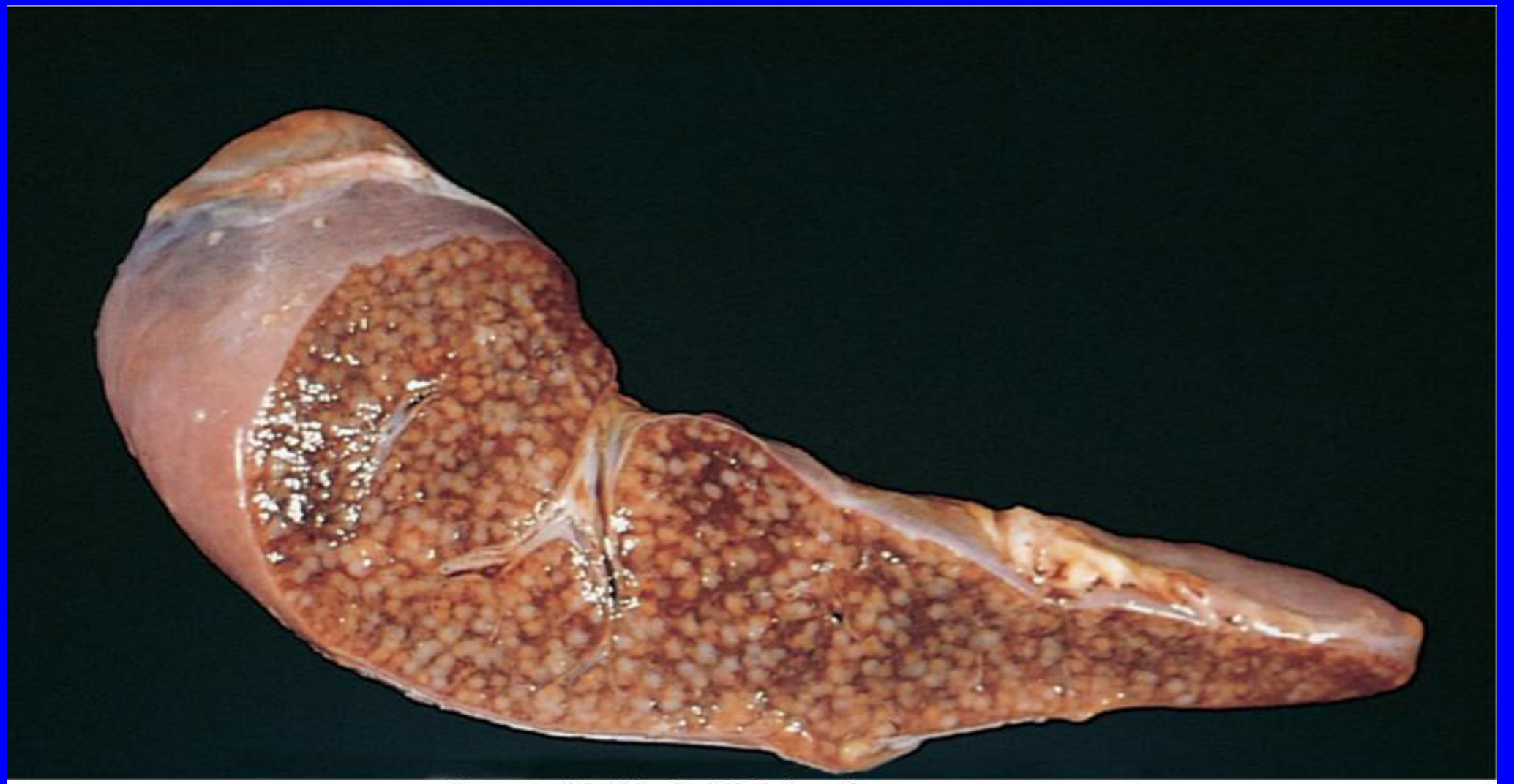
2. Systemic miliary tuberculosis

- 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

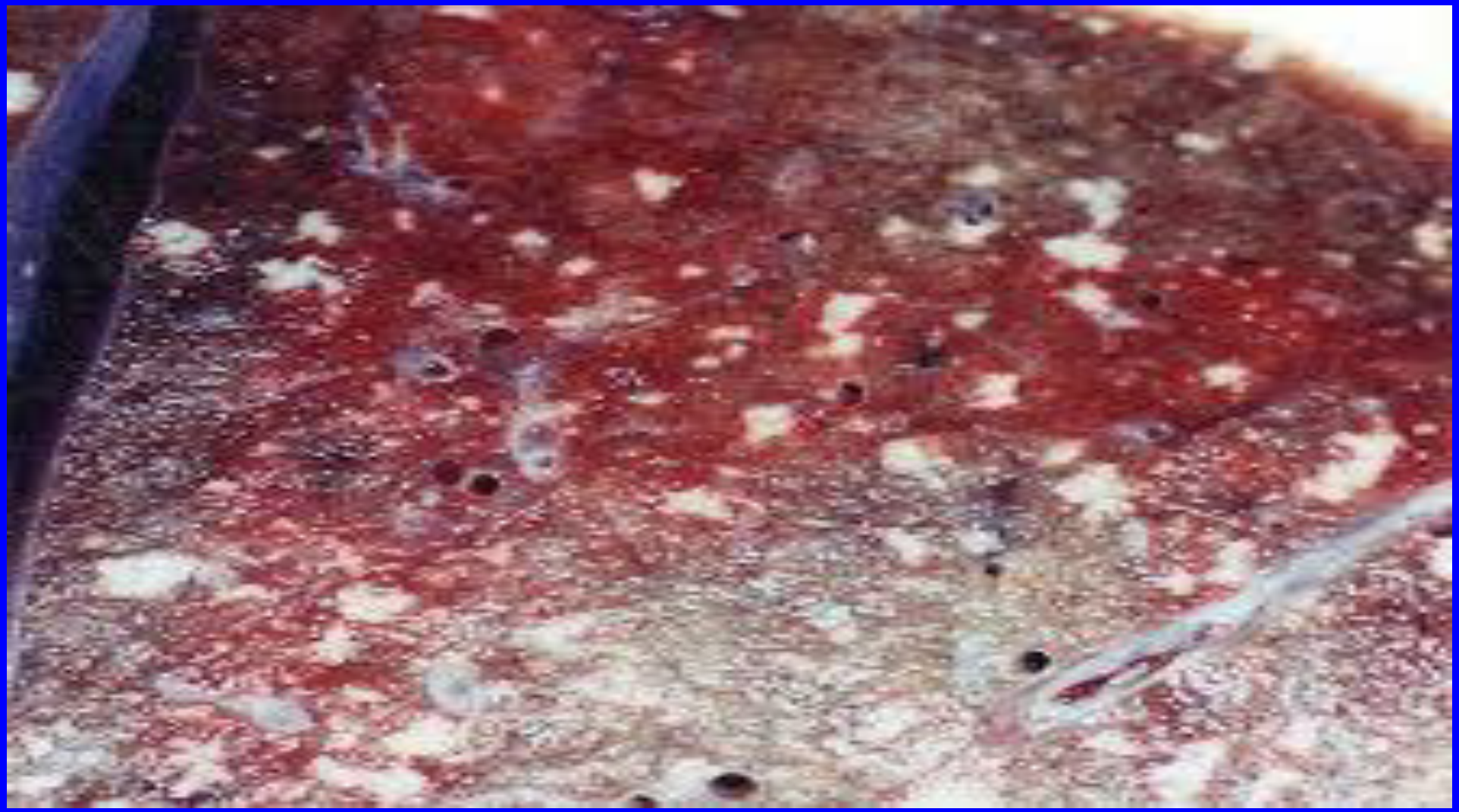
3. Isolated-organ tuberculosis

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

Miliary TB in spleen



Pulmonary MILIARY TB



- Paraspinal"cold" abscesses may track along the tissue planes to present as an abdominal or pelvic mass.

4. Lymphadenitis

- Is the most frequent form of extrapulmonary tuberculosis, usually occurring in the cervical region ("scrofula").
- Usually focal
- In HIV patients: Multiple lymph nodes

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

- The diagnosis of pulmonary disease is based on the history and on physical and radiographic findings of *consolidation or cavitation in the apices of the lungs.*
- Ultimately, however, *tubercle bacilli must be identified*The most common methodology for diagnosis of tuberculosis remains demonstration of acid-fast organisms in sputum by acid-fast stains or by use of fluorescent auramine rhodamine

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- Conventional cultures for mycobacteria require up to 10 weeks, but liquid media-based radiometric assays that detect mycobacterial metabolism are able to provide an answer within 2 weeks.

- PCR amplification can be performed on positive liquid media, as well as on tissue sections, to identify the mycobacterium. However, culture remains the standard diagnostic modality because it can identify the occasional PCR-negative case and also allows testing of drug susceptibility