Respiratory System Module
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Tuberculosis

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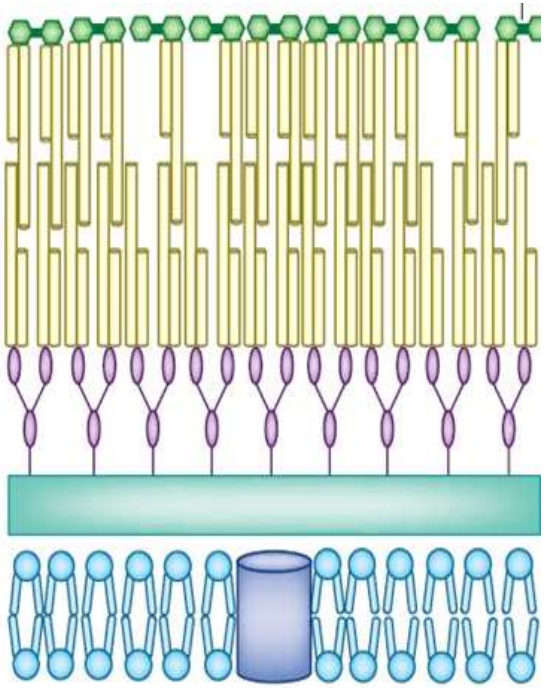
General characteristic of *M. tuberculosis*

1. Weakly Gram-positive bacilli
2. Nonmotile, obligate aerobes
3. Nonspore forming
4. The lipid mycolic acids make up more than 60% of the total cell wall mass (for which the mycobacteria are named)
5. Facultative intracellular pathogens usually infect phagocytes (e.g. macrophages).
6. The infection dose (ID) 10 organisms.



Pathogenesis

Source of Infection:

- Human (e.g. cases of pulmonary tuberculosis)
- Bovine (e.g. consumption of unpasteurized milk)

Mode of infection

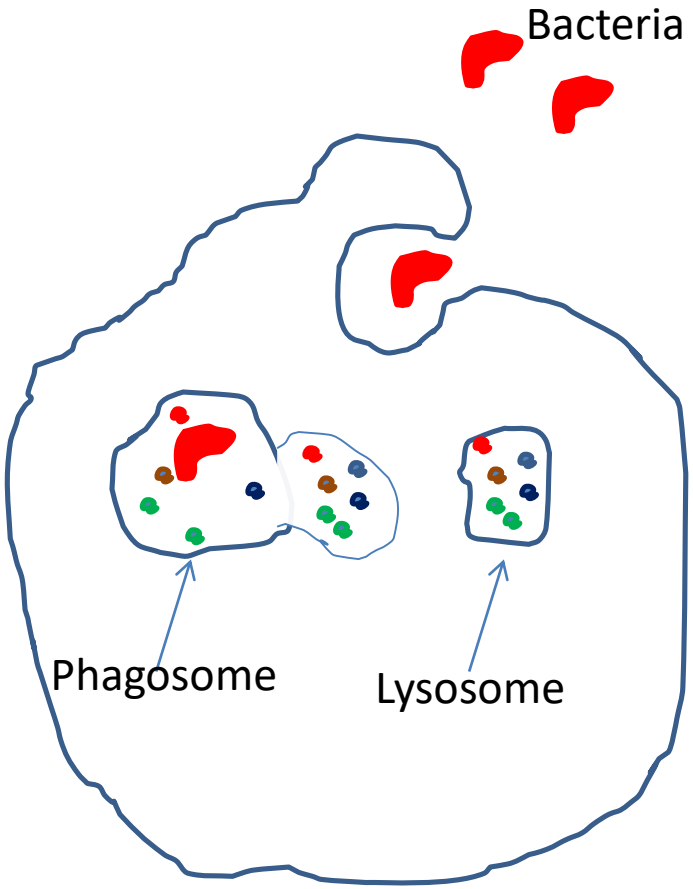
1. **Inhalation mode:** tuberculosis is an airborne disease (<5 µm in diameter) while coughing, sneezing, or speaking of infected patients.
2. **Inoculation mode:** the transmission through direct skin contact with an infected patient is uncommon.

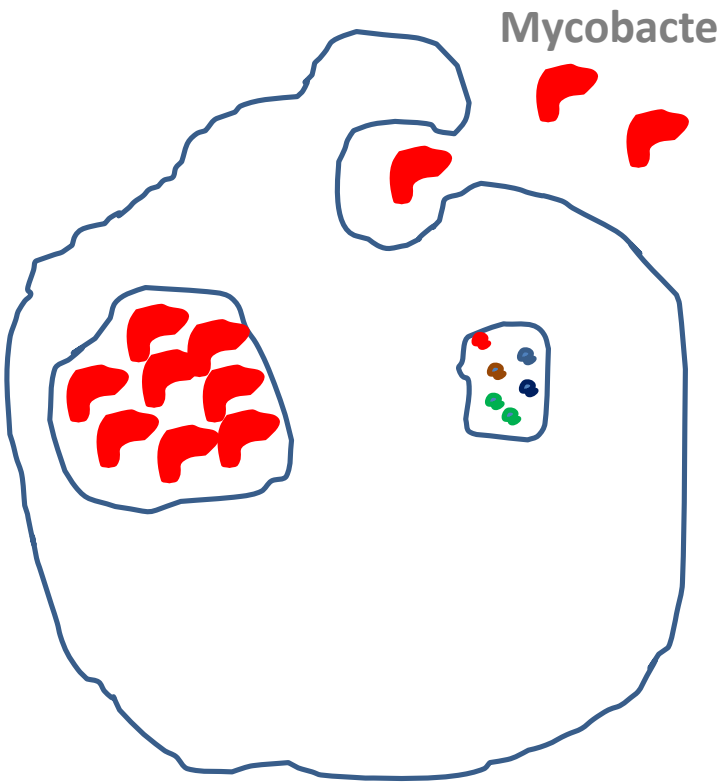
Risk factors

- Low immunity patients (AIDS)
- Post-transplantation (renal, cardiac), diabetes, smoking, IV drug abuse, chronic renal failure

Pathogenesis of TB

Q: Why do Mycobacteria can survive inside macrophages?





- Mycobacteria inhibits phagosome lysosome fusion
- Bacteria will multiply
- Macrophage will burst
- Proteolytic enzymes will released outside causing tissue destruction

Pathogenesis of TB

Classification of tuberculosis

Exposure

1° infection

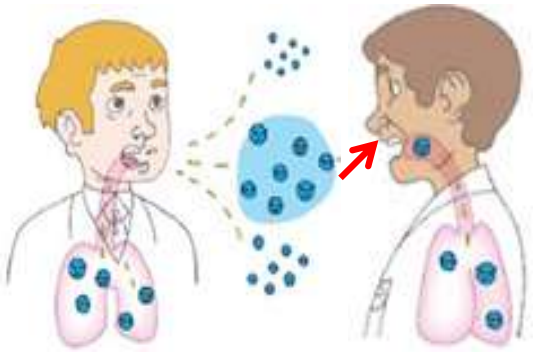
95%

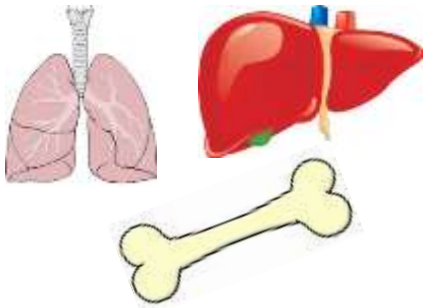
Healing

5%

Local pulmonary progression

Miliary TB





5% undergo 2° TB (reactivation)

Due to

- HIV
- Transplantation
- DM
- Smoking
- Others
- Malnutrition

Pathogenesis of TB

Primary TB

1. Primary tuberculosis is the response to the initial infection in an individual **not previously infected and sensitized** to *Mycobacterium*
2. Droplet containing tubercle bacilli are deposited in the peripheral respiratory alveoli
3. Tubercle bacilli are engulfed by **nonspecifically activated** alveolar macrophages.
4. The majority of individuals show resistance to infection and are able to contain the infection
5. Macrophages are activated by the cytokines at the site of infection. They be will able to kill and digest the tubercle bacilli.
6. These activated macrophages will aggregate around the center of the lesion and form a characteristic granuloma called tubercles

Pathogenesis of TB

Types of granulomas:

A. **Hard tubercles**: tubercles are initially hard, composed of a central zone of activated macrophages (epitheloid and giant cells) and peripheral zone of lymphocytes and fibroblast

B. **Soft tubercles**: later the central part of the lesion undergoes caseous necrosis, and in contains necrotic tissues resembling soft cheese

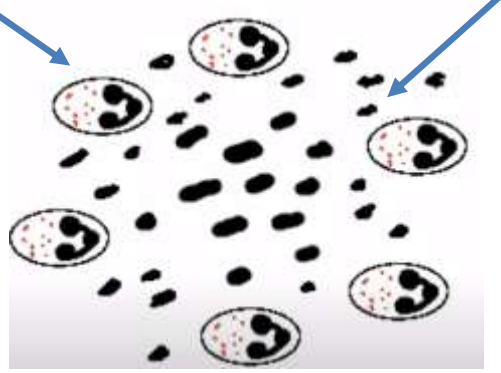
Growth of the *M .tuberculosis* is inhibited within this necrotic environment because of low oxygen tension and low pH. Eventually the lesion heals and calcifies. The viable bacilli may remain dormant within the macrophages or within necrotic material for many years without causing further tissue destruction

In a minority of cases, especially associated with the risk factors the macrophage activating response will be weak and the bacilli will be more virulent leading to secondary and reactivation infection.

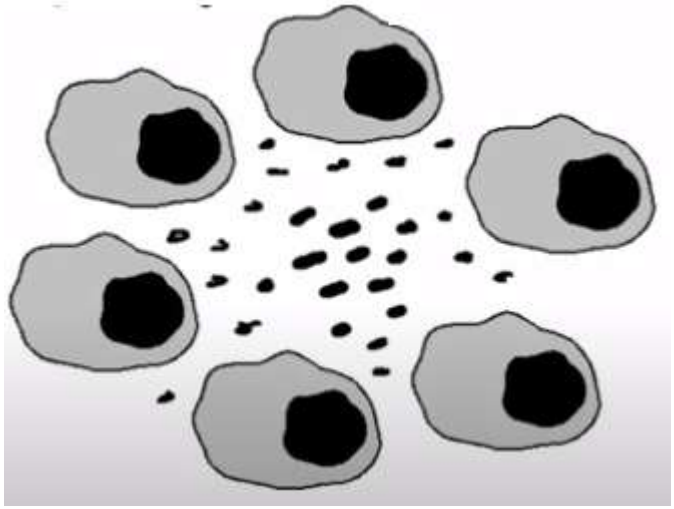
Primary TB

PMNs

Tubercle bacilli

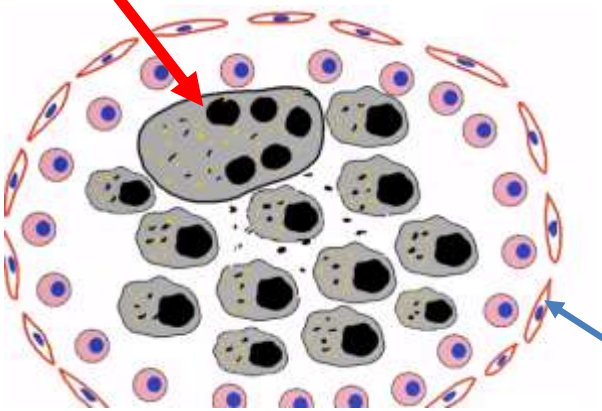


24 h

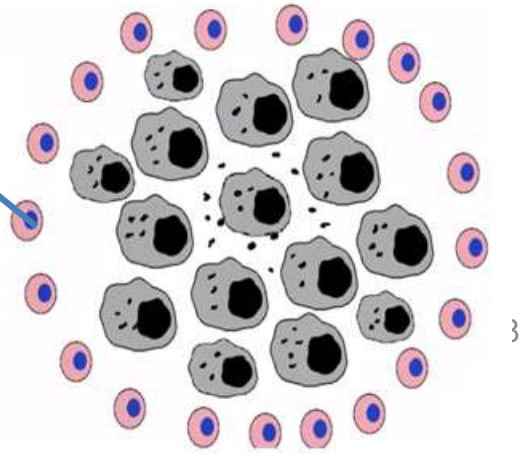


1st week

Giant cells

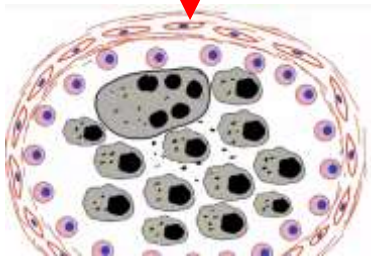


T- lymphocytes
- Migration inhibition factor
- Chemotactic factors
- Minimal amount of cytotoxic lymphokines



2 weeks

Fibroblast



Fibrosis

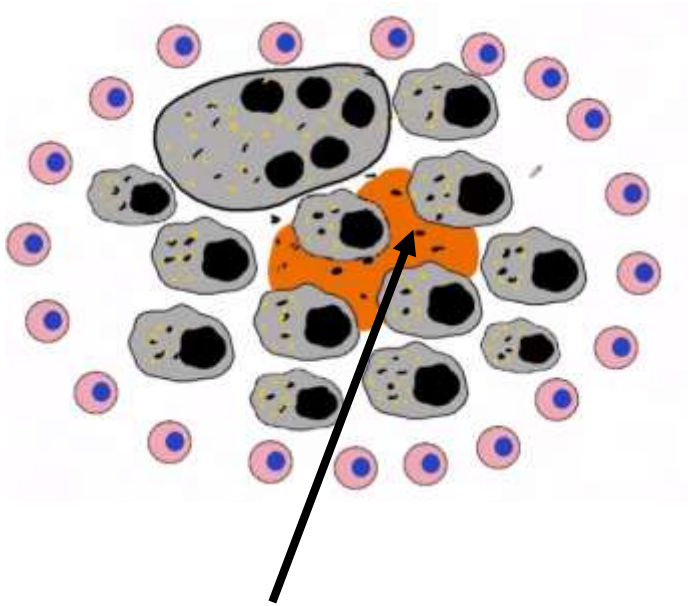
Mild necrosis

Secondary TB

The secondary response will be aggressive compared to the primary response due

1- Ischemia (No blood vessel in the tubercle).

2- Massive amount of cytotoxic lymphokines



Caseous Necrosis (sever)
-Massive amount of cytotoxic lymphokines

Pathogenesis of TB

Primary TB

Manifestations of Primary TB

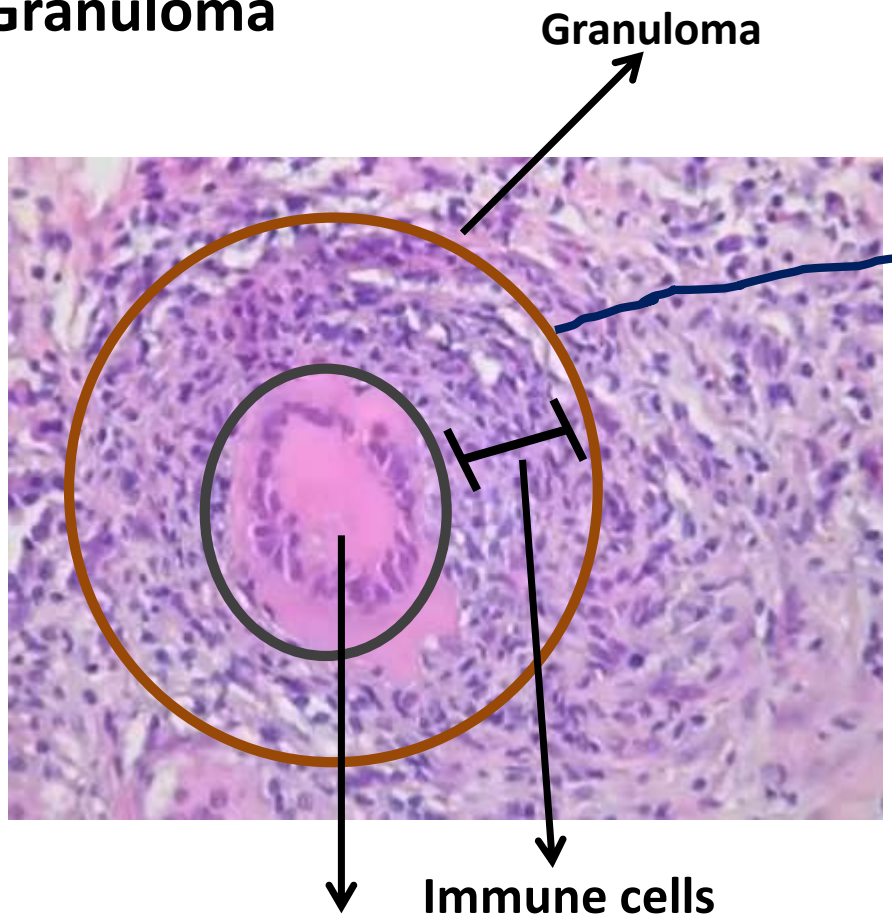
- May be symptom-free, or the individual may experience a flu-like illness.
- This can lead to delays in seeking care and results in transmission of the bacteria to others.
- **Healing in 3 weeks with fibrosis ± calcification**

Primary TB = Latent TB

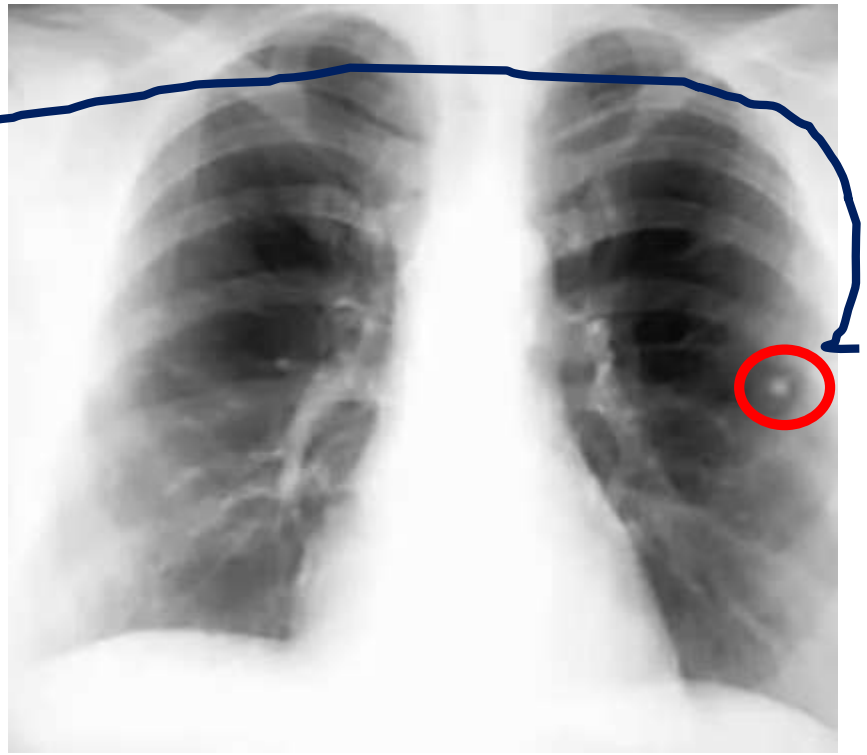
Pathogenesis of TB

Primary TB

Granuloma



Necrosis (dead macrophages and cells)



Calcified granuloma

Pathogenesis of TB

Secondary (reactivation) tuberculosis

1. Occurs in 5% of patients had primary tuberculosis
2. The risk factors associated with **reactivation including**
   A. Weakened immune system including:
   B. Poverty and drug abuse
   C. Smoking

3. Reactivation usually occurs in body areas of relatively high oxygen tension and low lymphatic drainage, most often in the apex of the lung.

Pathogenesis of TB

Secondary (reactivation) tuberculosis

4. The caseous necrosis becomes liquefied which containing a large number of bacilli which further spread by three ways:

- Direct drainage into the airways and then get discharge into the environment while coughing and talking
- Lymphatic spread
- Hematogenous spread to various organs

5. The lesions show spreading and resulting in a large pulmonary cavity and bronchial spread

Pathogenesis of TB

Secondary (reactivation) tuberculosis

Manifestations of secondary TB

1. Cough is the common symptom
2. It is initially dry, but as the disease progresses sputum is produced and mixed with blood (hemoptysis).
3. Fever, malaise, fatigue, sweating, and weight loss
4. Radiographically, lung cavities with progressive destruction of lung tissue.

Cough

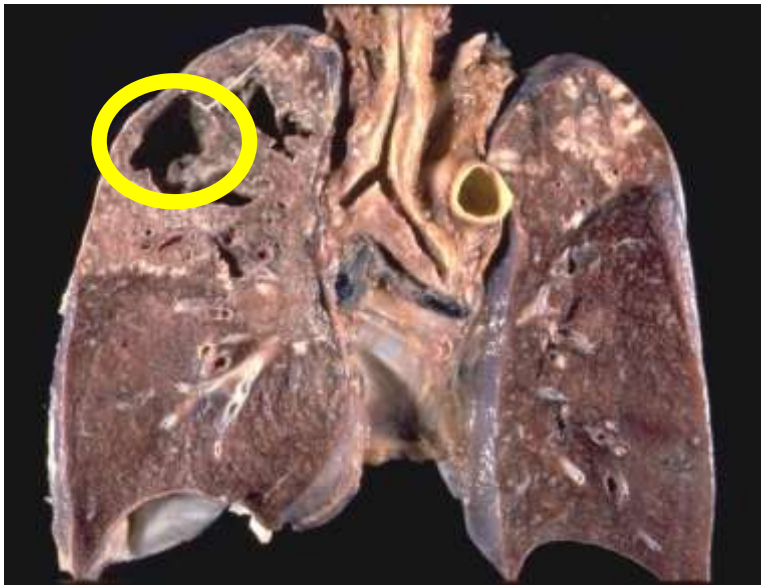
Blood stained sputum

Fever

Weight loss

Night sweats

Secondary (reactivation) TB



Pathogenesis of TB

Local Progressive Pulmonary TB

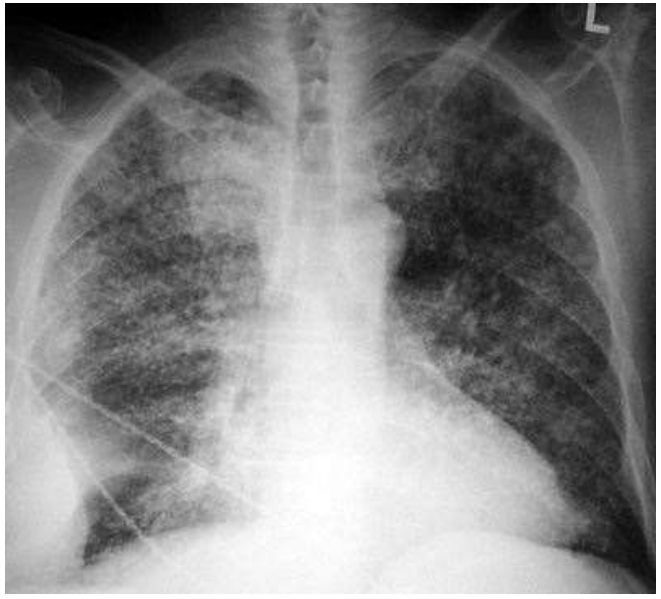
1. This can occur after primary or secondary TB
2. Occurs by the local extension to an entire lobe or segment

Disseminated (miliary) TB

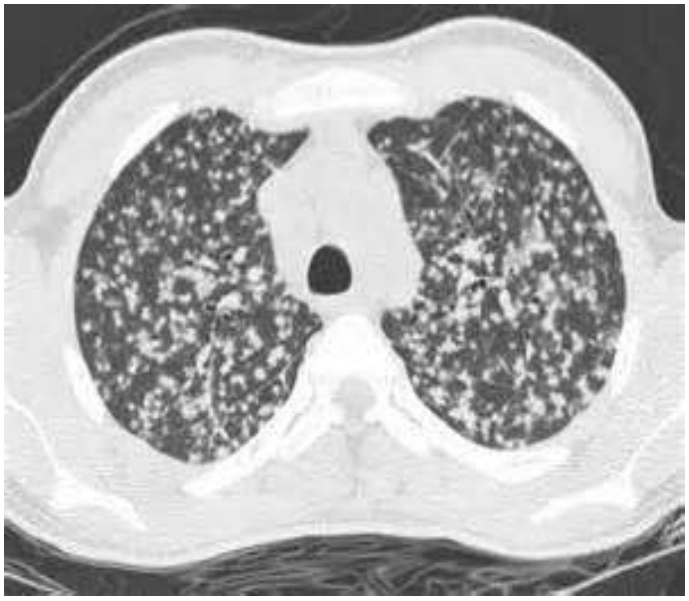
1. Miliary pulmonary disease
2. Spread through trachea to larynx leads to Laryngeal TB
3. Swallowing infected sputum leads to intestinal TB
4. Spread through pulmonary veins → Heart → arteries → systemic miliary TB .

Pathogenesis of TB

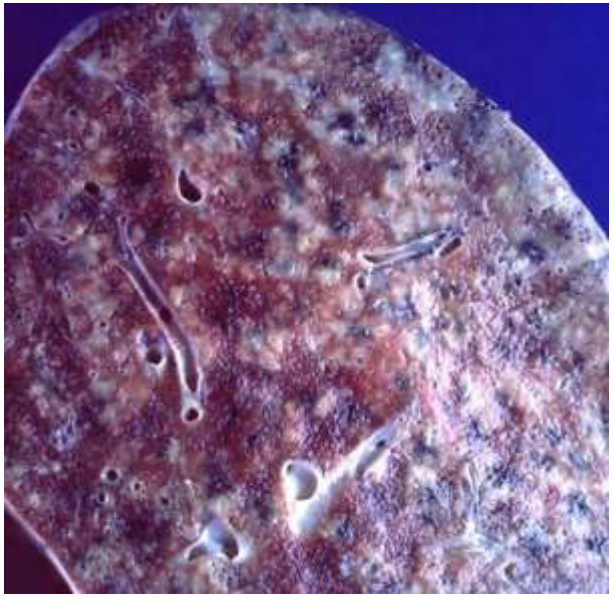
Miliary TB



X-ray of lung with miliary TB

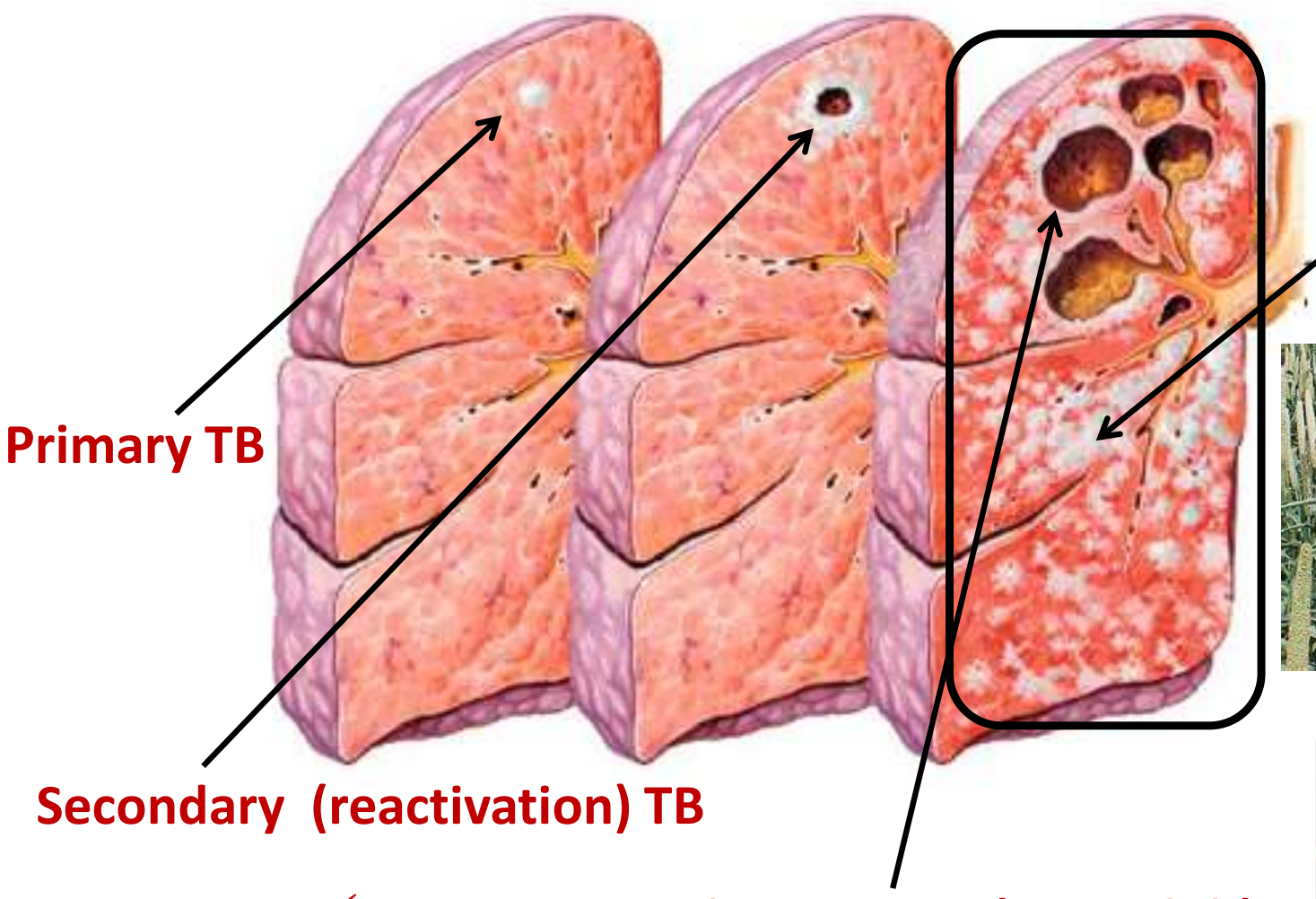


CT scan of lung with miliary TB



Lung miliary TB

Pathogenesis of TB



Primary TB

Miliary TB

Secondary (reactivation) TB

✓Progressive Pulmonary TB (entire lob)

Millet

Millet seeds

Who is a TB Suspect?

"Any person who presents with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks)."

Diagnosis

Diagnosis of active Tuberculosis

Diagnosis of latent Tuberculosis

Diagnosis

Diagnosis of active Tuberculosis:

Specimen collection:

1. In pulmunary tuberulosis:

a. The specimen is collected in a wide-mouth container, two specimens

- ✓ Sample collected on the same day
- ✓ Sample collected on the next day (early morning)

b. Laryngeal swabs or bronchial washing

c. In children, gastric aspirate my be used as they tend to swallow sputum

2. In extrapulmyonary tuberculosis (depending on te site of infection):

- ✓ Lymph node aspirate
- ✓ Pleural fluid
- ✓ Urine
- ✓ Synovial fluid
- ✓ CSF

Diagnosis

1- Diagnosis of active Tuberculosis (Explained in the lab):

2- Diagnosis of latent Tuberculosis (tuberculin test):

Principle

Latent tuberculosis is diagnosed by demonstration of type IV (delayed) hypersensitivity reaction against the tubercule bacilli antigens

Antigens used in tuberculin test

PPD (purified protein derivative antigen): it is a purified preparation of the active M. tuberculosis proteins after growing on a semisynthetic medium

Dosage

It is expressed in the tuberculin unit (TU). One TU is equal to 0.01 ml of 0.00002 mg of PPD

Procedure

Mantoux test: 0.1 ml of PPD containing 1 TU is injected intradermally into the flexor surface of the forearm.

Reading after

It is taken afetr 48-72 hours. At the site of inoculation, and induration surrounded by erythema is produced. If the width of induration is:

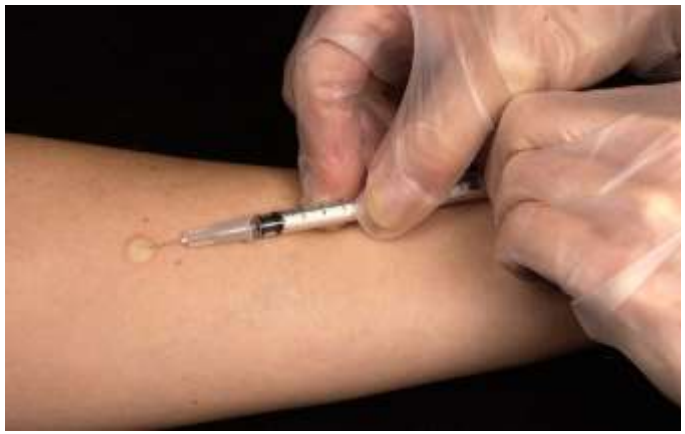
≥ 10 mm: Positive (tuberculin reaction)

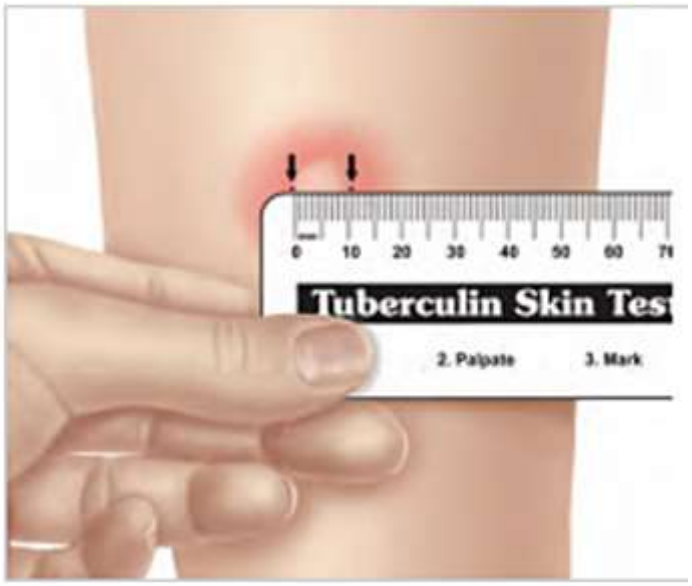
6-9 mm: Equivocal/ doubtful reaction

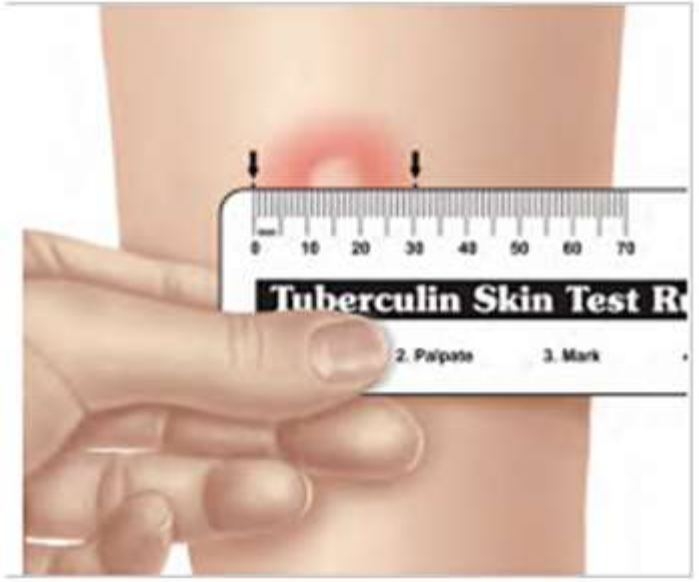
< 5 mm: Negative reaction

Diagnosis

Mantoux test







Reading the Mantoux tuberculin skin test: (left, correct) only the induration is being measured; (right, incorrect) the erythema is being measured.

Prevention

1. prompt detection of infectious patients
2. **Stay home : E**specially in the first few weeks of treatment for active tuberculosis
3. airborne precautions
4. treatment of people who have suspected or confirmed TB disease.
5. **Wear a mask (N95)**
6. **Vaccinations**

Prevention

Vaccinations

1. **The only available vaccine is bacillus Calmette-Guérin (BCG).**
2. **Bacillus Calmette-Guérin** (**BCG**) is a live attenuated strain of Mycobacterium bovis.
3. M. bovis is most commonly found in cattle and other animals such as bison, elk, and deer
4. **BCG vaccine :**
   - It is a live freeze-dried vaccine which must be reconstituted
   - Administered intra-dermally at the deltoid region on the left side
   - Dose: 0.05 ml
   - should immunize infants and under 5 years with single dose of BCG

Treatment

Treatment of latent TB :

- Isoniazid for 9 months .
- Rifampin for 4 months .

Treatment of Active TB :

- Isoniazid + Rifampin for 9 months .
- pyrazinamide + levofloxacin for 6-12 months .
- Rifampin + pyrazinamide for 2 months .

Interpretation of x-ray and skin test results

	X-ray	Mantoux test	Interpretation	
Sick patient suspected of having TB: ➢Fever ➢Hemopt-ysis ➢Other symptoms	Positive	Positive	Mostly have TB	**All should be confirmed by lab investigations**
	Positive	Negative	Negative skin test due to: 1. Not caused by TB 2. False negative test due to • personal error • False procedure	
	Negative	Positive	Negative x-ray might be due to extrapulmonary TB	

Case study

23-year-old man presented with a **4-weeks history of coughing**, **Shortness of breath** and **malaise**. He had lost **4kg in weight**, had **history of night sweating and haemoptysis.**

On examination

- 37.8°C but had
- No signs of nasopharyngeal infection
- Clear Lung sounds. No other physical signs.
- Chest X-ray showed bilateral upper- and middle-lobe shadowing

Lab tests

- High CRP
- Sputum was found to contain acid-fast bacilli and M. tuberculosis was subsequently cultured.

Diagnosis

- A diagnosis of *pulmonary tuberculosis* was made.
- The patient was treated with specific antibiotics