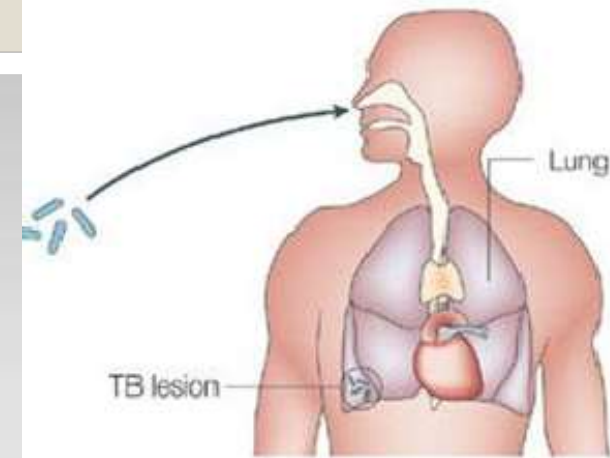


- A 27 year old female from a village has been having a cough, voluminous sputum production, and fever for the last few weeks. She has had a 5kg weight loss and feels very weak.

- What is the diagnosis?

- How will you investigate?

- How will you treat?



PULMONARY TUBERCULOSIS

**Prof. Mutti Ullah Khan
Head of Department
Medical Unit-II
Holy Family Hospital
Rawalpindi Medical College**

TUBERCULOSIS (T.B)

- Is the most prevalent communicable infectious disease on earth and remains out of control in many developing nations.
- It is a chronic specific inflammatory infectious disease caused by *Mycobacterium tuberculosis* in humans.
- Usually attacks the lungs but it can also affect any parts of the body.

TUBERCULOSIS (TB)

➤ **Coinfection with HIV**

- Accelerates the progression of both diseases.
 - Requiring rapid diagnosis and treatment of both diseases.
- Tuberculosis can produce atypical signs and symptoms in infants, the elderly, and immunocompromised hosts and it can progress rapidly in these patients.

ETIOLOGY

➤ **Mycobacterium tuberculosis**

- It presents either as latent TB infection (LTBI) or as progressive active disease.
- The latter typically causes progressive destruction of the lungs, leading to death in most patients who do not receive treatment.
- Common cause other than tuberculosis includes:
 - *M. avium intracellulare*, *M. scrofulaceum*
 - *M. ulcerans*, *M. fortuitum*, etc.

EPIDEMIOLOGY

- Roughly one of every three people on earth is infected by M. tuberculosis **(WHO, 2008)**.
- The distribution is very uneven, with the highest incidences found in southern Asia and sub-Saharan Africa.
- **In the United States**, about 13 million people have LTBI, evidenced by a positive skin test [purified protein derivative (PPD)] but no signs or symptoms of disease.

EPIDEMIOLOGY

- Every year approximately 1.7 million people develop TB.
- Tuberculosis (TB) kills about 2 million people each year.
- With the spread of AIDS, tuberculosis continues to lay waste to large populations.
- The emergence of drug resistant organism threatens to make this disease once again incurable.

RISK FACTORS OF TUBERCULOSIS

- Low socioeconomic status
- Crowded living conditions
- Diseases that weakens immune system like HIV
- Person on immunosuppressants like steroid Health care workers
- Migration from a country with a high number of cases
- Alcoholism
- Recent Tubercular infection (within last 2 years)

COINFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV)

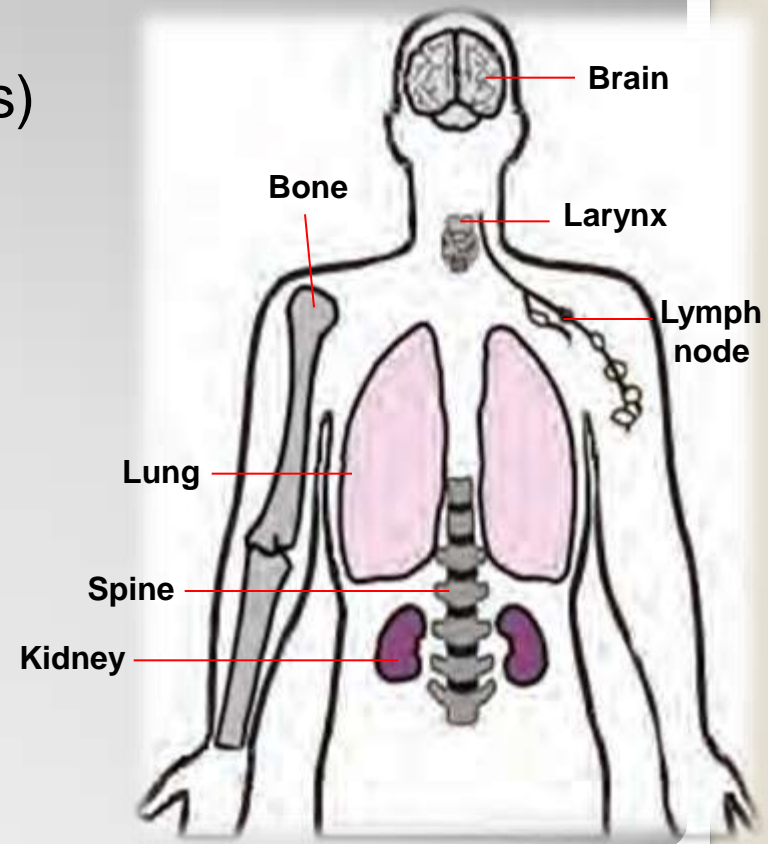
- HIV is the most important risk factor for active TB, because the immune deficit prevents patients from containing the initial infection.
- Roughly 10% of US TB patients are coinfecting with HIV, **and** roughly 20% of TB patients ages 25 to 44 years are coinfecting with HIV.

SITES INVOLVED

➤ **Pulmonary TB** (85% of all TB cases)

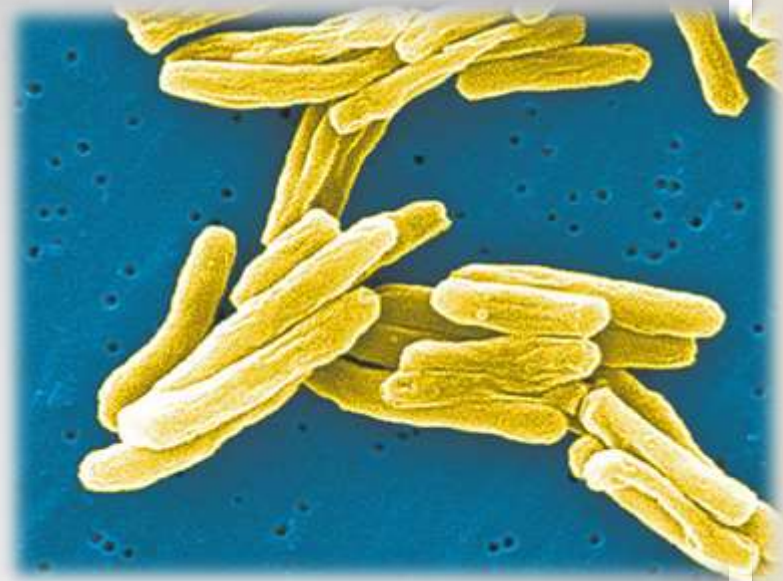
➤ **Extra-pulmonary sites**

- Lymph node
- Genito-urinary tract
- Bones & Joints
- Meninges
- Intestine
- Skin



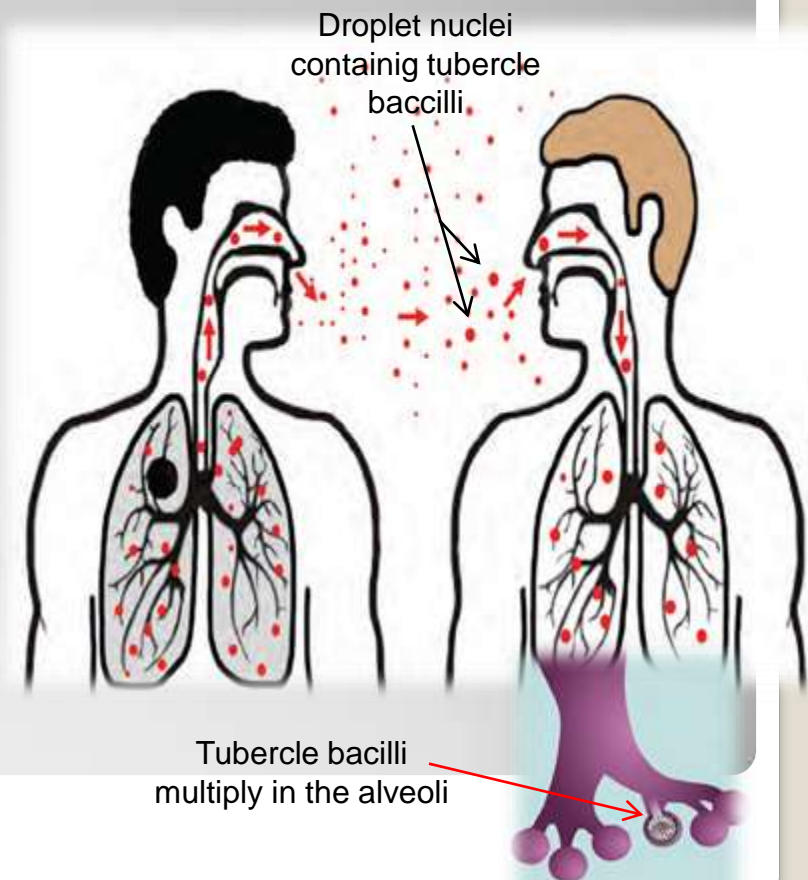
CHARACTERISTICS OF M. TUBERCULOSIS

- Rod shaped,
- 0.2-0.5 μ in D, 2-4 μ in L
- Mycolic acid present in its cell wall, makes it acid fast
- It resists decolourization with acid & alcohol
- Aerobic and non motile
- It multiplies slowly, can remain dormant for decades



How is TB Transmitted?

- **Person-to-person** through the air by a person with active TB disease of the lungs
- Less frequently transmitted by:
Ingestion of **M. bovis** found in unpasteurized milk
- **Inoculation** (in skin tuberculosis)
- **Transplacental route** (rare route)



PRIMARY TUBERCULOSIS

Primary Infection

- The progression to clinical disease in a previously unexposed, immuno-competent person depends on **three factors**:
 - (1) The number of *M. tuberculosis* organisms inhaled
 - (2) Infecting dose and the virulence of these organisms
 - (3) The development of anti-mycobacterial cell-mediated immunity**
- Immunity to *M. tuberculosis* is primarily mediated by **T_H1** cells, which stimulate macrophages to kill the bacteria

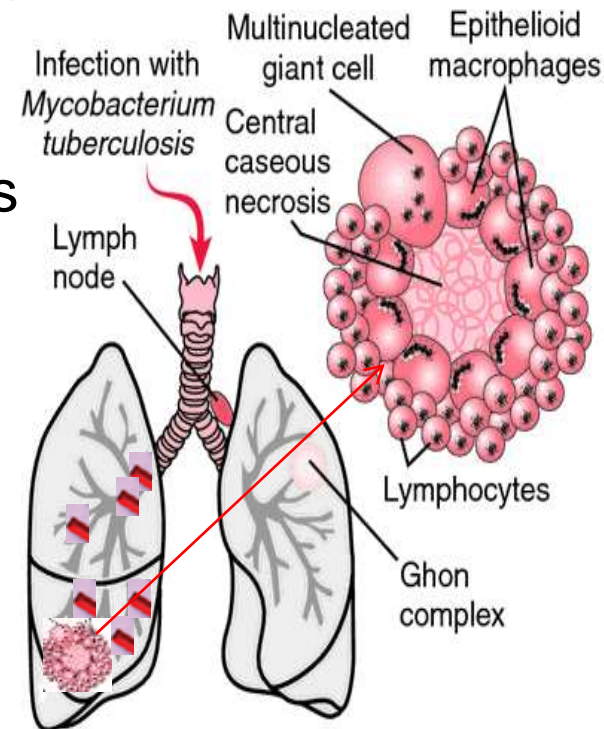
PRIMARY TUBERCULOSIS

➤ **Disease that develops in a previously unexposed person.** Almost always begins in lungs

➤ Inhaled bacilli implant in the distal airspaces of lower part of upper lobe or upper part of lower lobe

➤ 1-1.5 cm area of grey white inflammation with consolidation develops, called as

Ghon focus which often caseates



PRIMARY TUBERCULOSIS

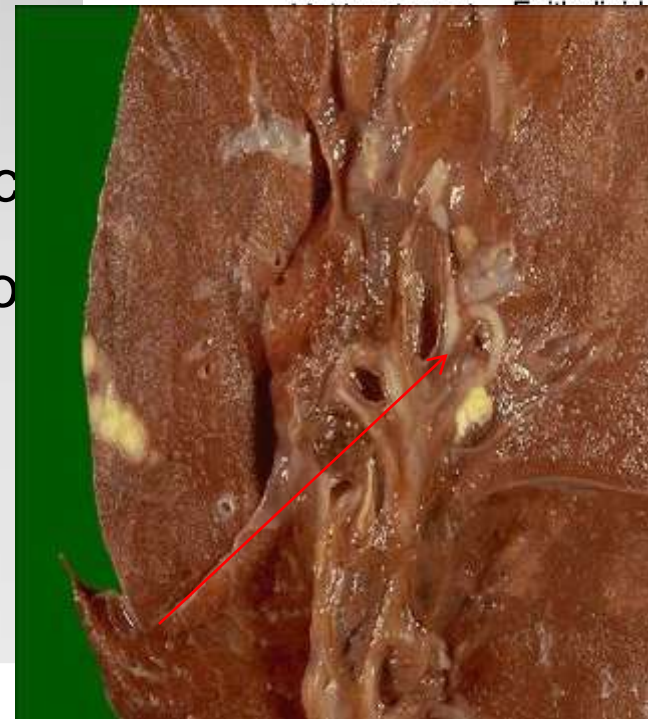
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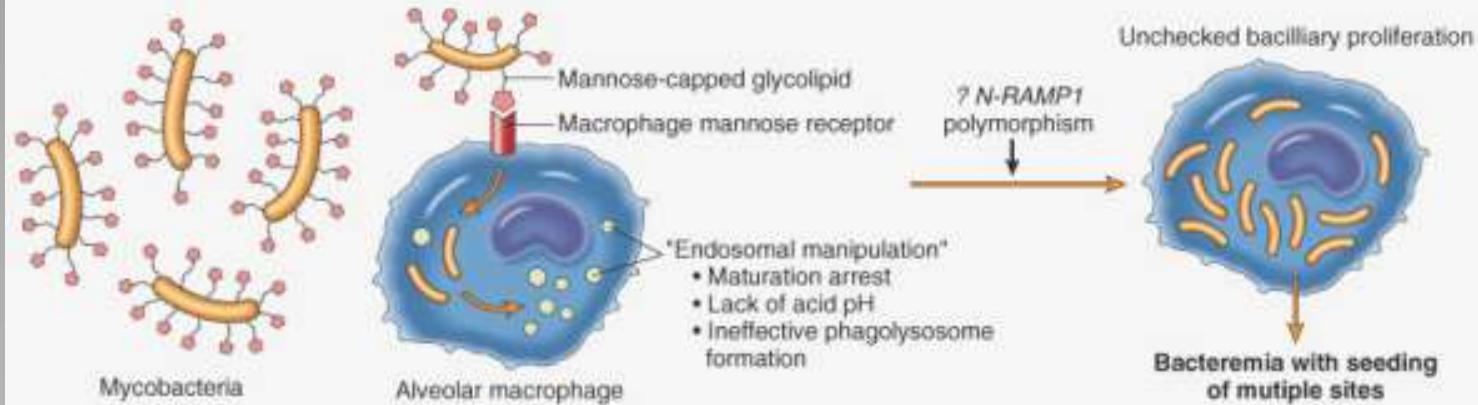
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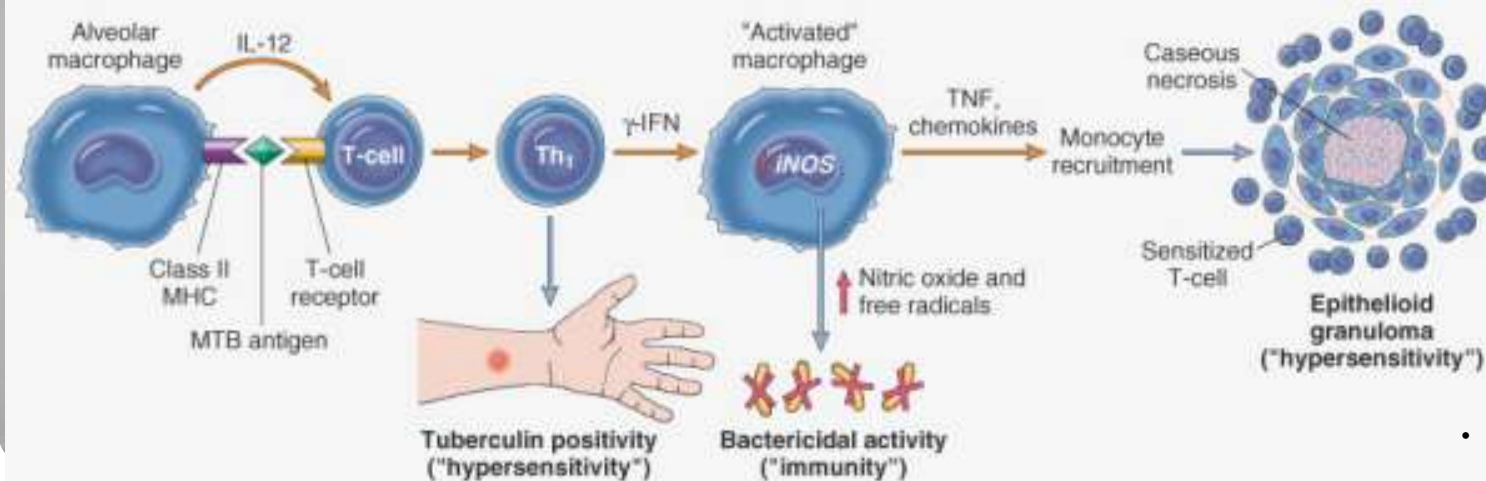
Ghon focus which often caseates



A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)



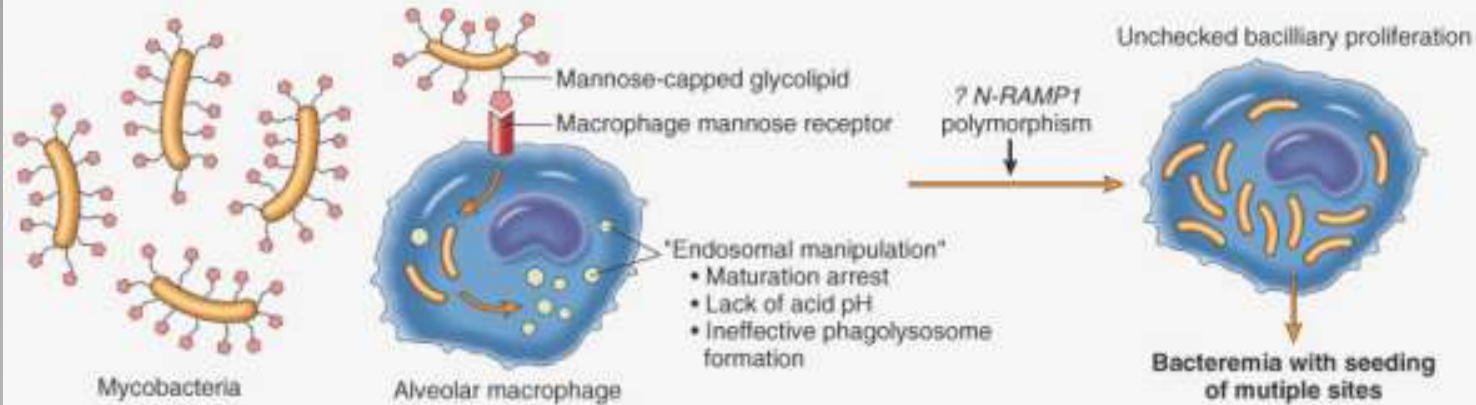
B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)



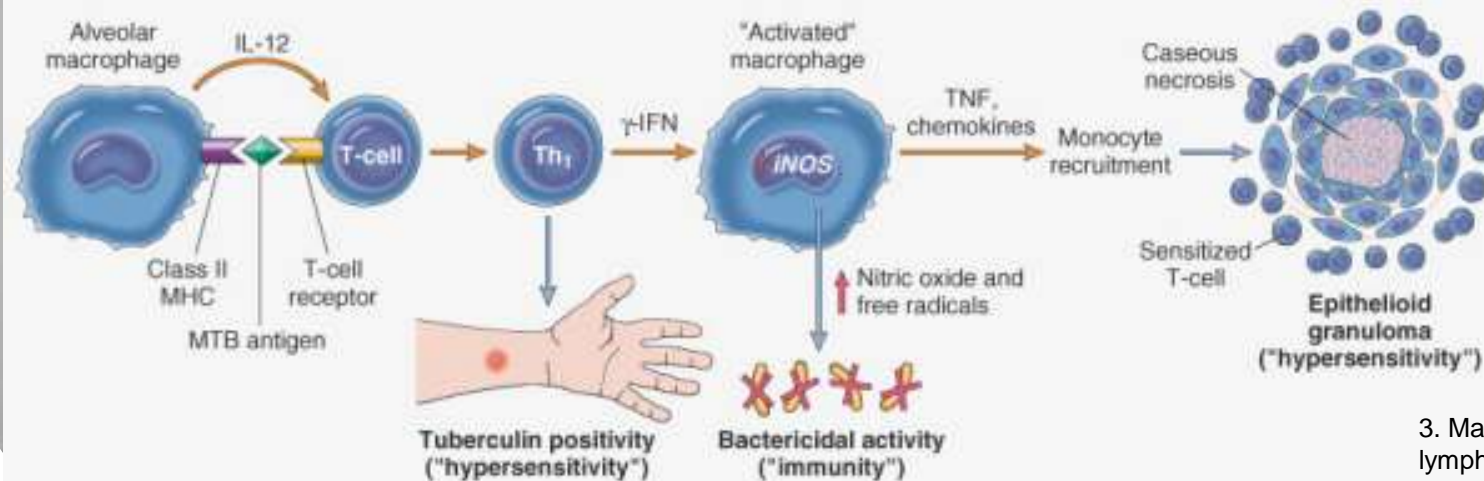
- Inhibition of Ca²⁺ signals and blocking recruitment
- Assembly of the proteins which mediate phagosome-lysosome fusion

1. *M. tuberculosis* enters macrophages by endocytosis mediated by several macrophage receptors: mannose receptors bind lipoarabinomannan, a glycolipid in the bacterial cell wall
2. Inside the macrophage, *M. tuberculosis* replicates within the phagosome by blocking phagolysosome formation

A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)



B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)



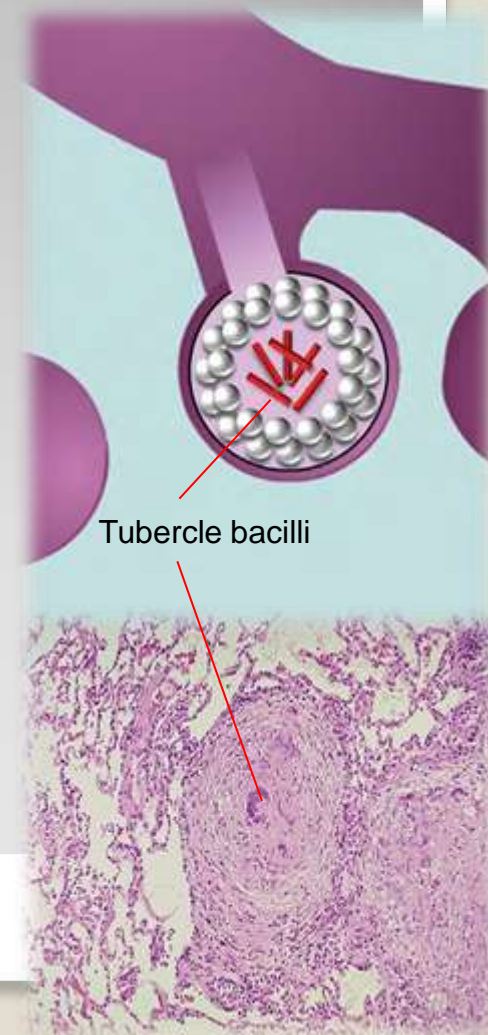
1. About 3 weeks after infection, a T_H1 response against *M. tuberculosis* is mounted that activates macrophages to become bactericidal.
2. Differentiation of T_H1 cells depends on the presence of IL-12, which is produced by antigen presenting cells

3. Mature T_H1 cells, both in lymph nodes and lung, produce IFN- γ . IFN- γ is the critical mediator which drives macrophages to become competent to contain the *M. tuberculosis* infection.

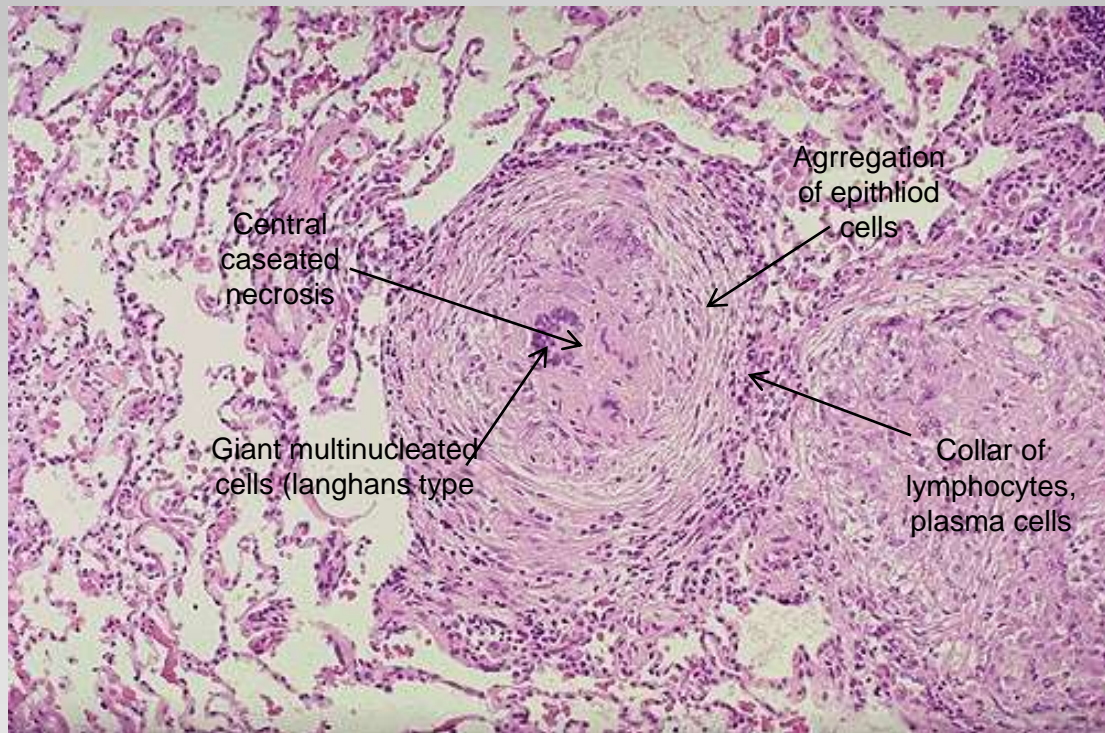
PRIMARY TUBERCULOSIS

Histopathological changes

- Granulomatous inflammation forms both caseating and non caseating tubercles
- Tuberculous granuloma has the following criteria:
 1. Rounded outlines
 2. Central caseous necrosis
 3. Transformed macrophages called epithelioid cells
 4. Lymphocytes, plasma cells, and fibroblasts

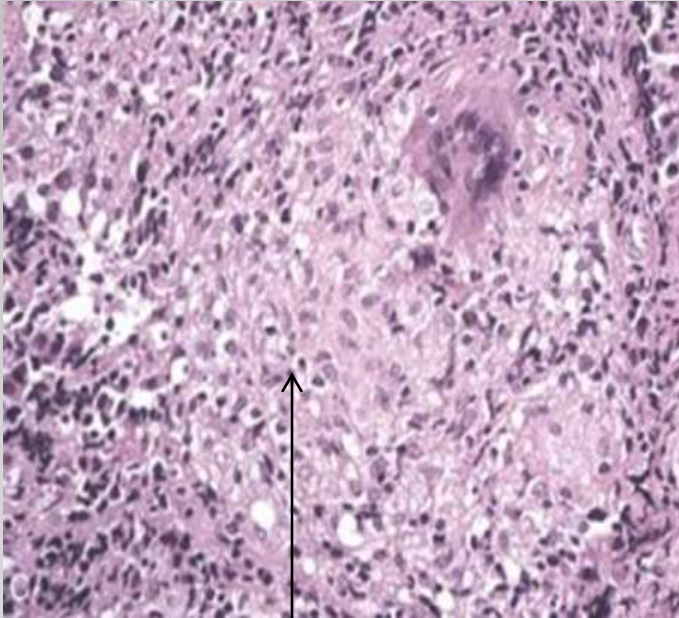


PRIMARY TUBERCULOSIS

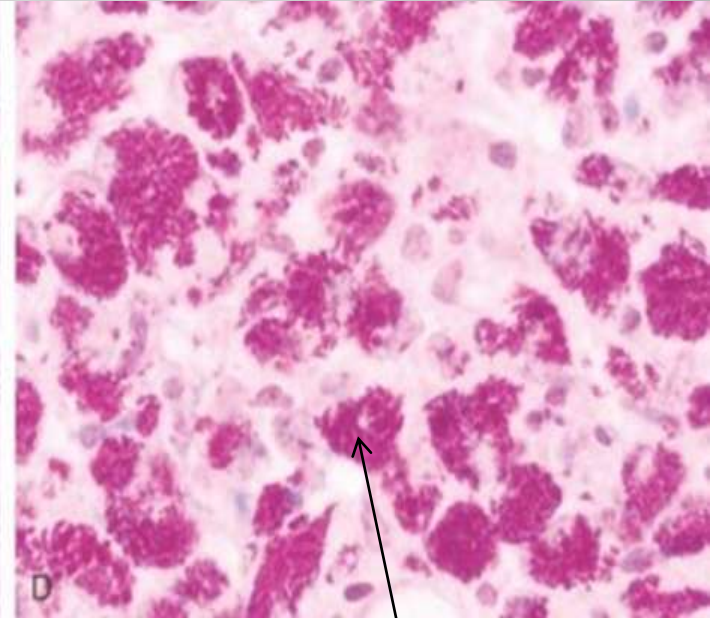


Well-defined granulomas. They have rounded outlines. The center contains several Langhans giant cells. Granulomas are composed of transformed macrophages called epithelioid cells along with lymphocytes, plasma cells, and fibroblasts. The localized, small appearance of these granulomas suggests that the immune response is fairly good

PRIMARY TUBERCULOSIS



Occasionally, even in immunocompetent individuals, tubercular granulomas might not show central caseation



In immunosuppressed individuals, tuberculosis may not elicit a granulomatous response ("nonreactive tuberculosis"); instead, sheets of foamy histiocytes are seen, packed with mycobacteria that are demonstrable with acid-fast stains

FATE OF PRIMARY TUBERCULOSIS

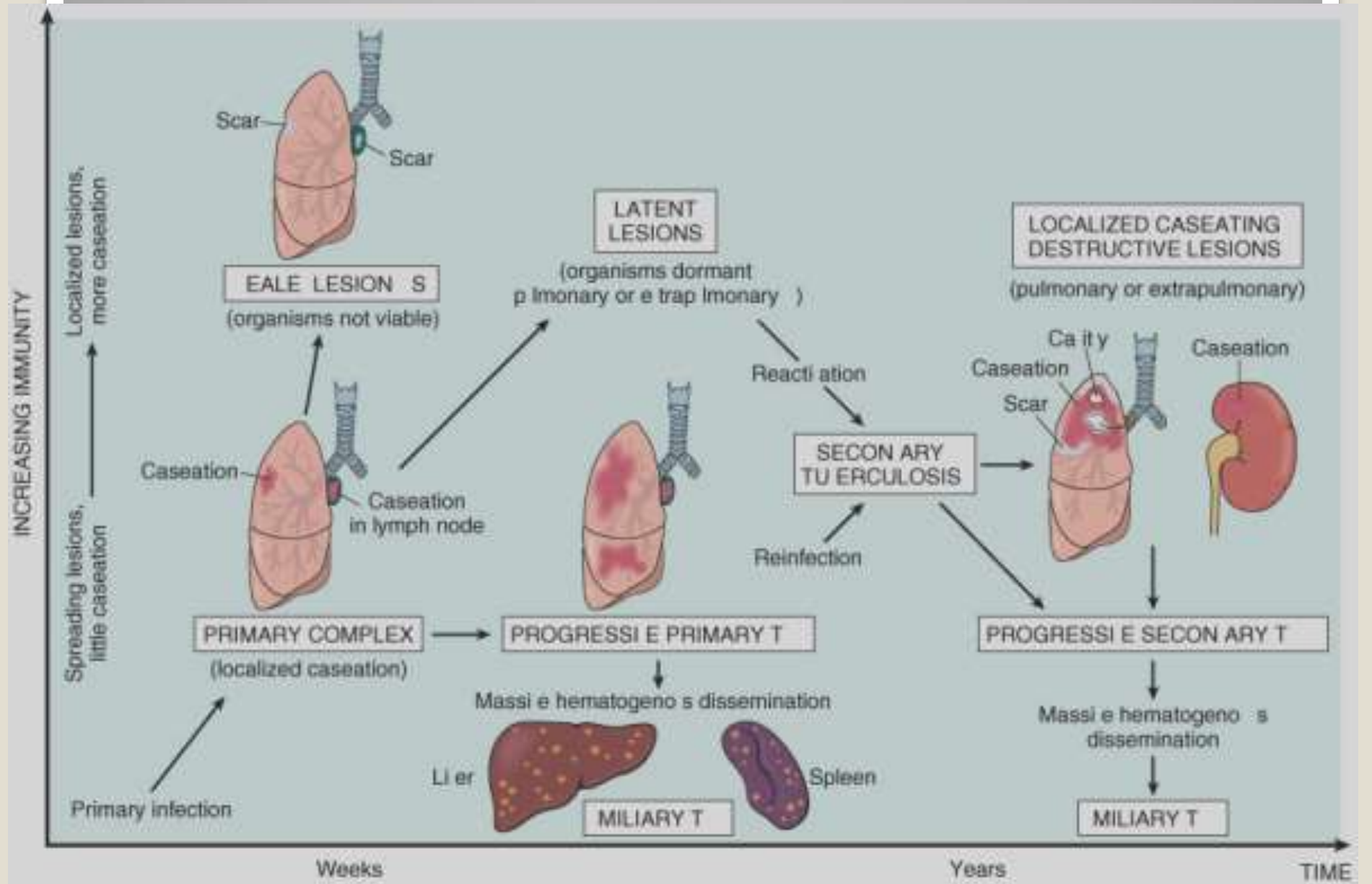
➤ No progression

- Healing by fibrosis and calcification
- **Ghons complex** after undergoing progressive fibrosis produces radiologically detectable calcification called as **Ranke complex**

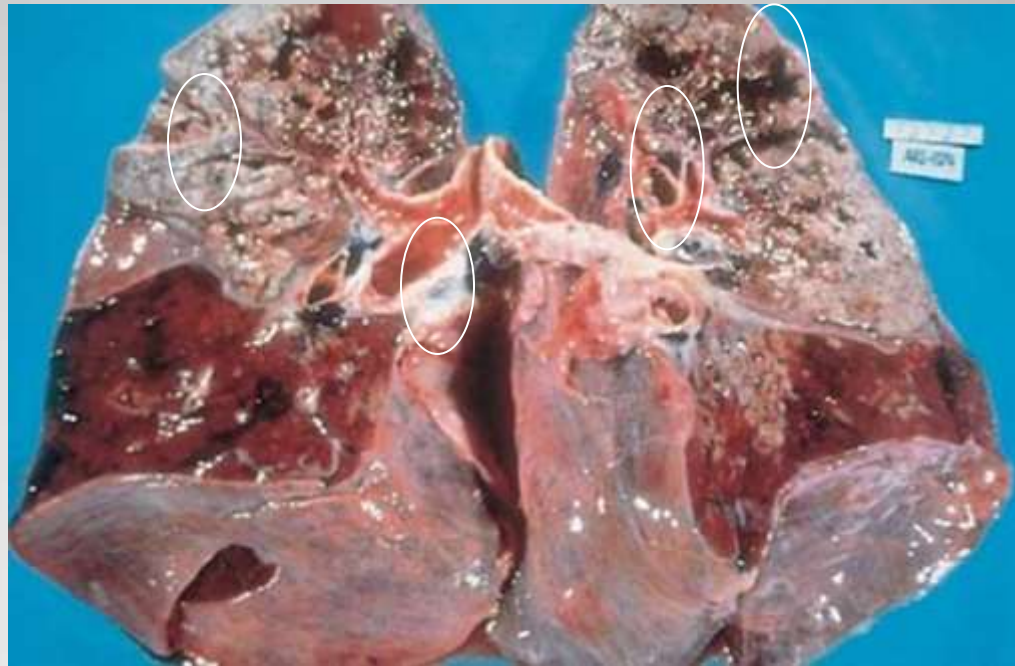
➤ Progressive primary tuberculosis

- Primary miliary tuberculosis
- Dissemination to organs like liver, spleen, kidney, ..etc.





SECONDARY PULMONARY TUBERCULOSIS



The upper parts of both lungs Showed:

- Gray-white areas of caseation
- Multiple areas of softening and cavitation

FATE OF SEC. PULMONARY TUBERCULOSIS

- The lesion may heal with fibrous scarring and calcification
- The lesions may coalesce together to form large area of tuberculous pneumonia and produce progressive secondary pulmonary tuberculosis producing pulmonary & extra pulmonary lesions:
 - Tuberculous caseous pneumonia
 - Fibrocaceous tuberculosis
 - Miliary tuberculosis

MILIARY TUBERCULOSIS

- Extensive infection via hematogenous spread
- **In lung:** lesions are either microscopic or small, visible foci (2mm) of yellow white consolidation scattered through out lung parenchyma
- **Miliary pulmonary disease** can cause pleural effusion, tuberculous empyema or obliterative fibrous pleuritis.
- **Extra pulmonary miliary tuberculosis** is most prominent in the liver, spleen, bone marrow, adrenals, meninges, kidneys, fallopian tubes and epididymis but can involve any organ

MILIARY TUBERCULOSIS



Miliary tuberculosis of the spleen

The cut surface shows numerous gray-white granulomas

EXTRA PULMONARY TUBERCULOSIS

- In tissues or organs seeded **hematogenously**
- Commonly involved organs include:
 - Intestinal tuberculosis (Primary, Secondary and hyperplastic)
 - Meninges (Tuberculous meningitis)
 - Kidneys (Renal tuberculosis)
 - Adrenals (Addison disease)
 - Bones (Osteomyelitis)
 - Vertebrae (Pott disease)
 - Fallopian tubes (Salpingitis)

TUBERCULOUS CASEOUS PNEUMONIA

- The caseous material from a case of secondary tuberculosis in an individual with high degree of hypersensitivity, may spread to rest of the lung producing caseous pneumonia.

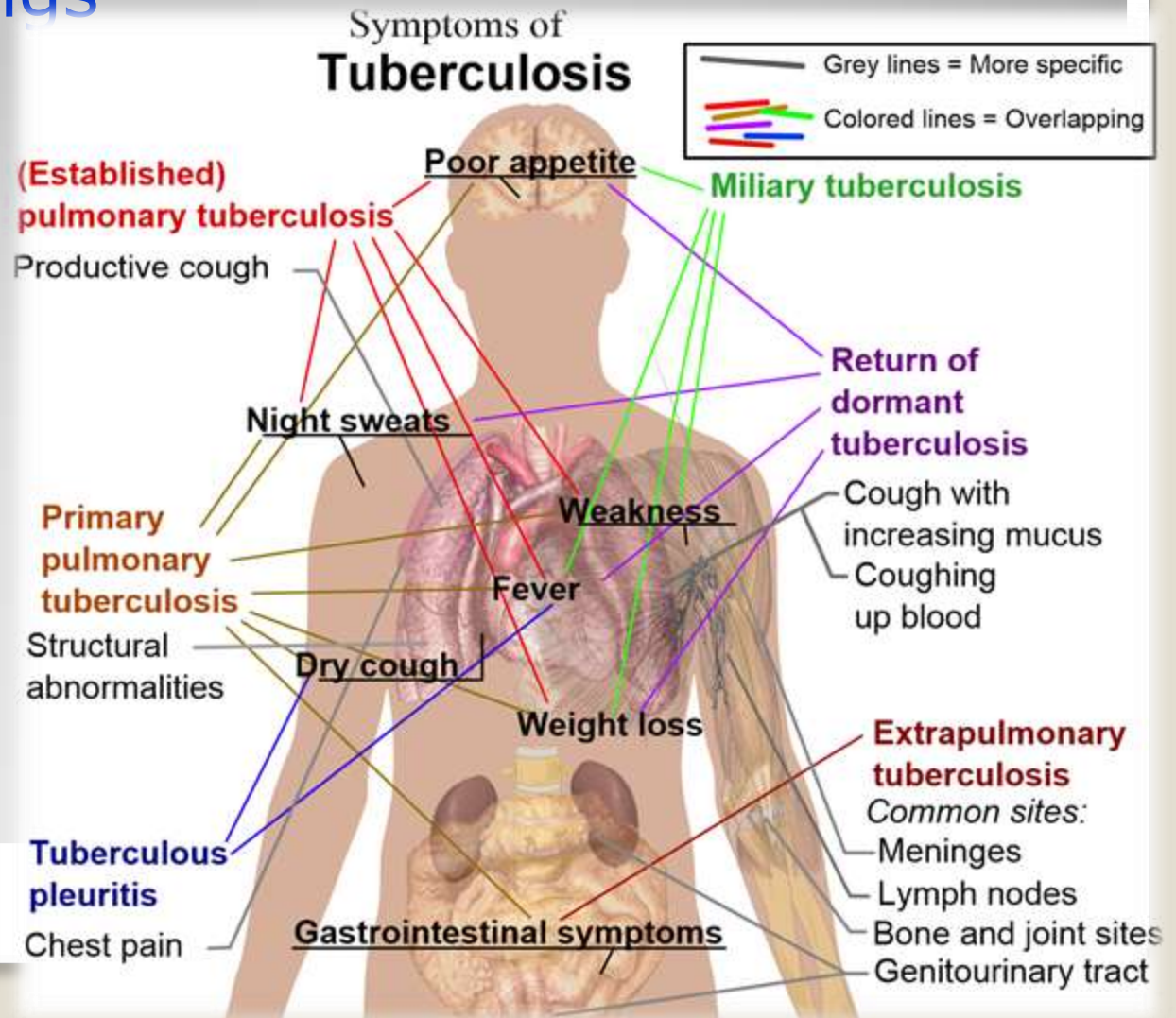
FIBROCASEOUS TUBERCULOSIS

- The original area of Tuberculous pneumonia undergoes massive central caseation necrosis which may-Break in to a bronchus forming a cavity called as Cavitory or Open Fibrocaceous TB
- and become the source of spread of infection to others (open tuberculosis).
- It can lead to endobronchial and endotracheal TB.
- Remain as a soft caseous lesion without drainage in to a bronchus or bronchiole to produce a non cavitory lesion called as Chronic Fibrocaceous TB.

Influence of HIV Infection on Pathogenesis

- HIV infection is the most important risk factor for active TB.
- As CD4+ lymphocytes multiply in response to the mycobacterial infection, HIV multiplies within these cells and selectively destroys them, gradually eliminating the TB-fighting lymphocytes
- HIV-infected patients infected with TB are at a substantially higher risk of early mortality compared with HIV-negative TB patients
- Most clinicians elect to begin TB treatment first. A reasonable time to begin HIV treatment is after 2 months of TB treatment

CLINICAL Findings



CLINICAL PRESENTATION OF TUBERCULOSIS

Signs and Symptoms

- Patients typically present with weight loss, fatigue, a productive cough, fever, and night sweats

Physical Examination

- Dullness to chest percussion, rales
- Auscultation revealed vocal fremitus sound

Laboratory Tests

- Moderate elevations in the white blood cell (WBC) count with a lymphocyte predominance

CLINICAL PRESENTATION OF TUBERCULOSIS

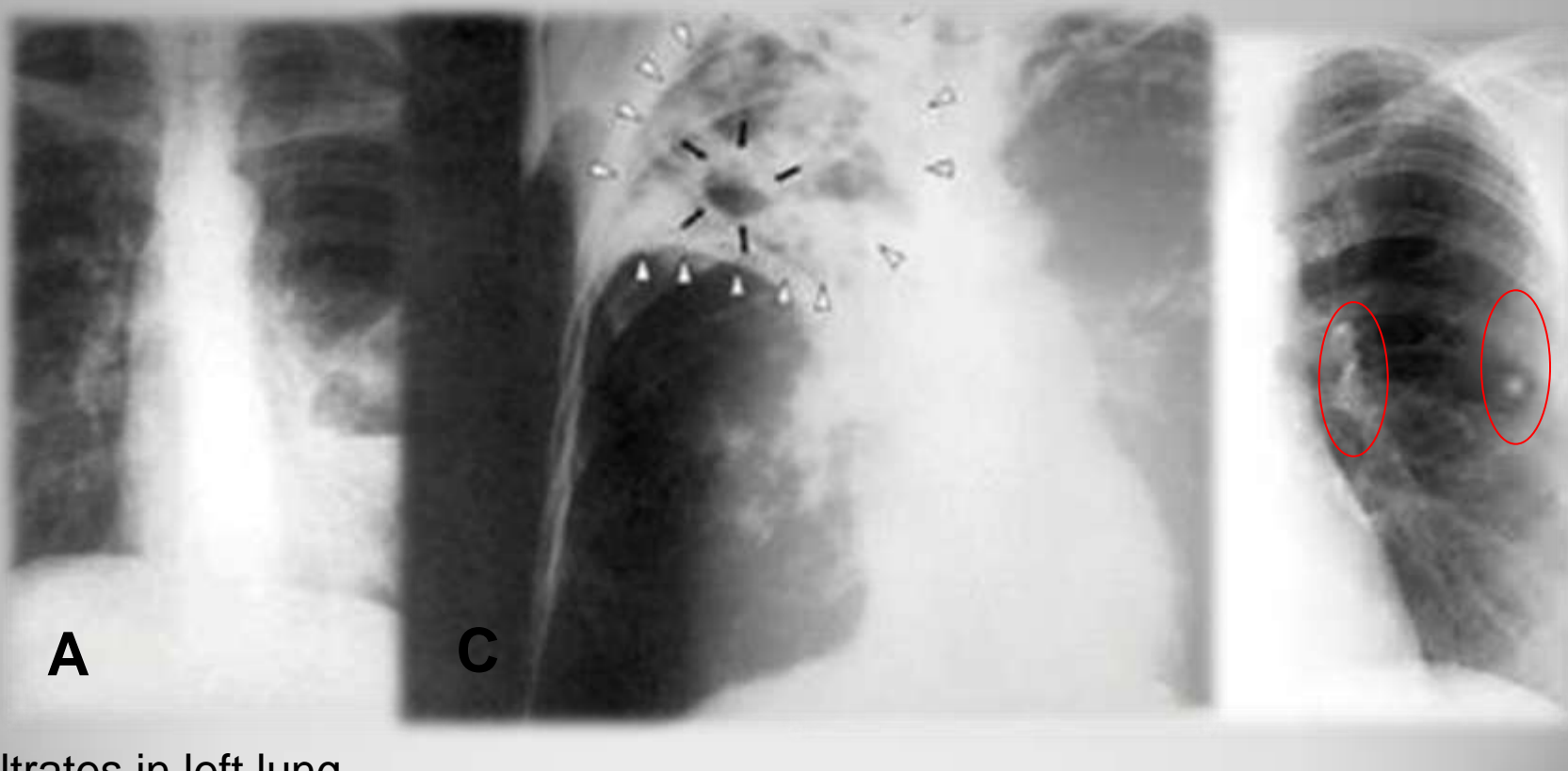
Chest Radiograph:

- Patchy or nodular infiltrates in the apical areas of the upper lobes or the superior segment of the lower lobes
- Cavitation that may show air-fluid levels as the infection progresses

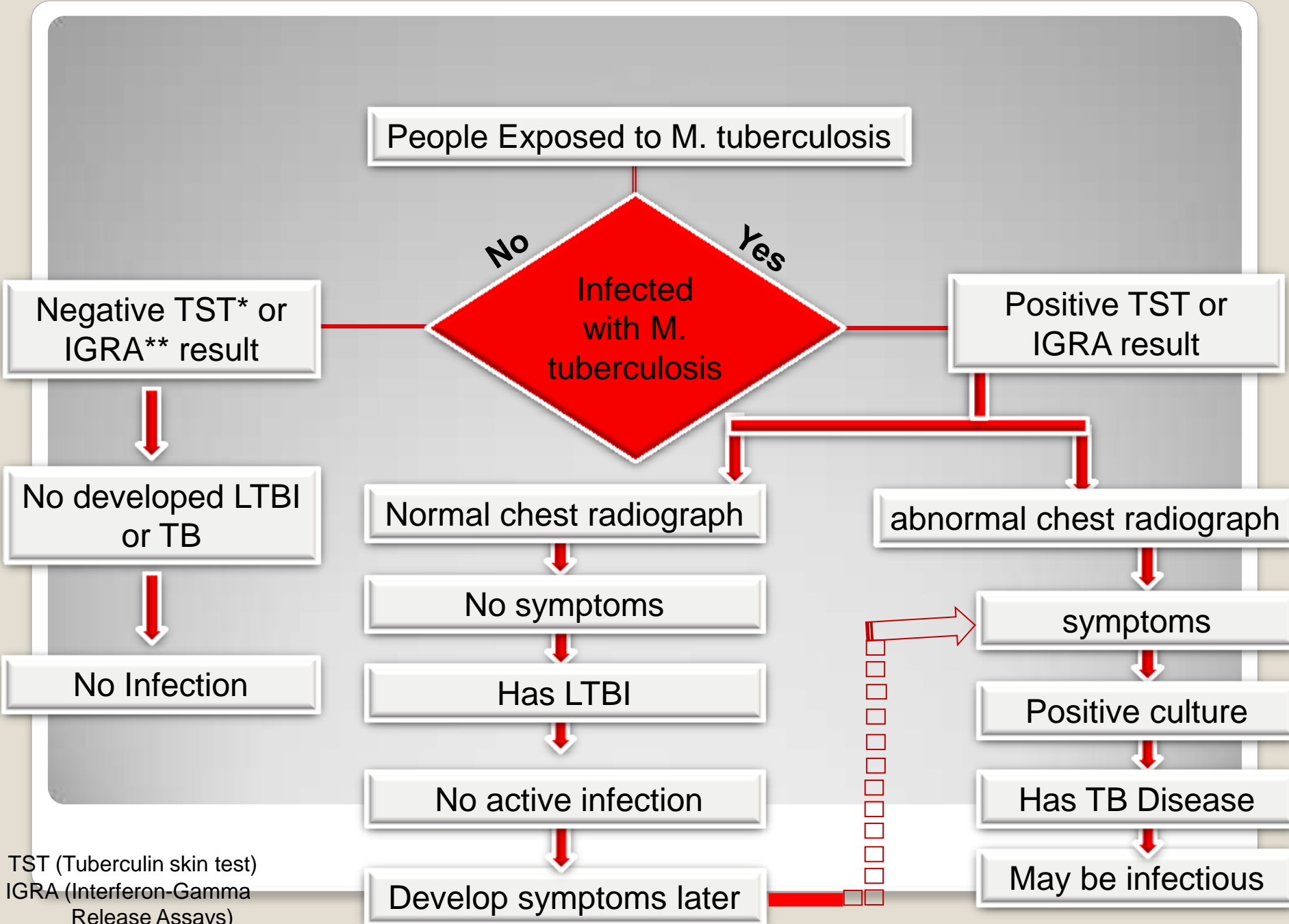
CT scan: To diagnose TB that has spread throughout the body (miliary TB) and to detect lung cavities caused by TB

MRI: This test looks for TB in the brain or the spine

Chest radiographs in pulmonary tuberculosis



- A. Infiltrates in left lung
- B. Ghon's complex (Primary tuberculosis)
- C. Bilateral advanced pulmonary tuberculosis and cavitation in apical area of right lung



* TST (Tuberculin skin test)
 * IGRA (Interferon-Gamma Release Assays)

DIAGNOSIS

SKIN TESTING



- Infection with *M. tuberculosis* typically leads to the development of delayed hypersensitivity to *M. tuberculosis* antigens, which can be detected by the tuberculin (Mantoux) test.
- About 2 to 4 weeks after infection, intracutaneous injection of purified protein derivative of *M. tuberculosis* (**PPD**) induces a visible and palpable induration that peaks in 48 to 72 hours .

DIAGNOSIS

- A positive tuberculin test result signifies cell-mediated hypersensitivity to tubercular antigens. It does not differentiate between infection and disease .
- False-negative reactions may be produced by certain viral infections, sarcoidosis, malnutrition, immunosuppression .
- False-positive reactions may also result from infection by atypical mycobacteria.

DIAGNOSIS

Sputum examination

- Are essential to confirm TB Best collected in morning before any meal
- Sputum examination on 3 days, increase chances of detection.
- Sputum can be collected from laryngeal swab or bronchial washing.
In small children, gastric lavage can be examined.
- Smear should be prepared from thick dirty part of sputum & stained with **Ziehl-Neelson technique**.

TREATING TB DISEASE (GENERAL PRINCIPLES)

- Always treat with multiple drugs. Never add a single drug to a failing regimen.
- Treatment course depends on the categories of the patient.
- Usually 6 months, sometimes 9 months.
- Four drugs for two months **Isoniazid – Rifampicin – Ethambutol – Pyrazinamide** .
- Two drugs for four or seven months **Isoniazid - Rifampicin** .
- **DOTS** (Directly Observed Treatment Short-course) is given .

TREATING LATENT INFECTION

- **Isoniazid** is the preferred drug for treating latent TB infection.
- Generally, isoniazid alone is given for 9 months for latent TB infection (LTBI) reduces a person's lifetime risk of active TB.

Drugs

- All first-line anti-tuberculous **drug names** have a standard three-letter and a single-letter abbreviation:
 1. ethambutol is EMB or E,
 2. isoniazid is INH or H,
 3. pyrazinamide is PZA or Z,
 4. rifampicin is RMP or R,
 5. Streptomycin is STM or S.

Drugs

- There are six classes of second-line drugs (SLDs) used for the treatment of TB. A drug may be classed as second-line instead of first-line for one of two possible reasons: it may be less effective than the first-line drugs.
 1. aminoglycosides: e.g., amikacin (AMK), kanamycin (KM);
 2. polypeptides: e.g., capreomycin, viomycin, enviomycin;
 3. fluoroquinolones: e.g., ciprofloxacin (CIP), levofloxacin, moxifloxacin (MXF);
 4. thioamides: e.g. ethionamide, prothionamide
 5. cycloserine (the only antibiotic in its class);
 6. p-aminosalicylic acid (PAS or P).

Drugs

- considered "third-line drugs"
- not very effective or because their efficacy has not been proven .
- Rifabutin is effective, but is not included on the WHO list because for most developing countries, it is impractically expensive.

1. rifabutin
2. macrolides: e.g., clarithromycin (CLR);
3. linezolid (LZD);
4. thioacetazone (T);
5. thioridazine;
6. arginine;
7. vitamin D;
8. R207910.

Monitoring and DOTS

- DOTS stands for "Directly Observed Therapy, Short-course" and is a major plan in the WHO global TB eradication programme.
- The DOTS strategy focuses on five main points of action.
 1. These include government commitment to control TB,
 2. diagnosis based on sputum-smear microscopy tests done on patients who actively report TB symptoms,
 3. direct observation short-course chemotherapy treatments,
 4. a definite supply of drugs, and
 5. standardized reporting and recording of cases and treatment outcomes.

Prevention

- TB prevention and control takes two parallel approaches.
- In the first, people with TB and their contacts are identified and then treated.
- Identification of infections often involves testing high-risk groups for TB.
- In the second approach, children are vaccinated to protect them from TB.

Vaccines

- Many countries use Bacillus Calmette-Guérin (BCG) vaccine as part of their TB control programs, especially for infants. According to the W.H.O., this is the most often used vaccine worldwide, with 85% of infants in 172 countries immunized in 1993.
- BCG provides some protection against severe forms of pediatric TB
- unreliable against adult pulmonary TB,
- Currently, there are more cases of TB on the planet than at any other time in history
- urgent need for a newer, more effective vaccine that would prevent all forms of TB—including drug resistant strains—in all age groups and among people with HIV.

Current Surgical Intervention

- Patients with hemoptysis first received Bronchial Artery Embolization because of the recurrent hemoptysis.
- Current indication of Lung Resection for **pulmonary tuberculosis** includes MDR-TB with a poor response to medical therapy, hemoptysis due to bronchiectasis or Aspergillus superinfection, and destroyed lung as previously reported, which are consistent with our indications.
- Surgery remains a crucial adjunct to medical therapy for the treatment of MDR-TB and medical failure lesions.

Questions

- What are the modes of transmission of TB?

- What is primary pulmonary TB?

- What is secondary pulmonary TB?

- Which sites can be involved in extrapulmonary TB?

- What is military TB?

- What are the investigations used to diagnose TB?

- How is TB treated?

***Thank you for your
attention***