



PATHOLOGY
TEAM 44



MED 444
KING SAUD UNIVERSITY



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Pathology Of Tuberculosis

COLOR INDEX:

MAIN TEXT (BLACK)

FEMALE SLIDES (PINK)

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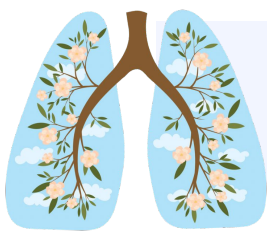
IMPORTANT (RED)

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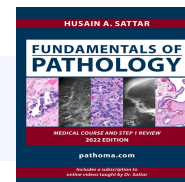


Objectives

-  Recognize the main causative microorganism of tuberculous infection and mode of transmission.
-  Understand the epidemiology and pathogenesis and the sequence of events in primary pulmonary tuberculosis.
-  Know the natural history and spectrum of tuberculosis.
-  Describe morphological changes (gross and microscopic) and morphologic spectrum of tuberculosis.
-  Describe the clinical features and the methodology for diagnosis.
-  Know the treatment and the progression of the disease.

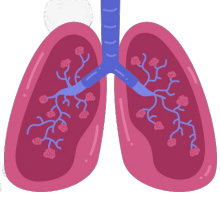
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Tuberculosis

Definition

Tuberculosis is a communicable **chronic** granulomatous disease caused by *Mycobacterium tuberculosis*. It usually involves the lungs but may affect any organ or tissue in the body. (Primary in the lung then disseminates)

Epidemiology

- Contracted by inhalation of *Mycobacterium tuberculosis* (TB)
- TB bacilli are strict aerobe, acid-fast (due to mycolic acid in cell wall).
- It is estimated that 1.7 billion individuals are infected by tuberculosis worldwide, with 8 to 10 million new cases and 1.5 million deaths per year.
- Tuberculosis flourishes under conditions of: poverty, crowding, and chronic debilitating illness

Certain disease states also increase the risk, such as:

1-Diabetes mellitus

2-Hodgkin's lymphoma

3-Chronic lung disease (particularly silicosis)

4-Chronic renal failure

5-Malnutrition, alcoholism, and immunosuppression

6-**HIV**: In areas of the world where HIV infection is prevalent, HIV infection is **the dominant risk factor** for the development of tuberculosis

Etiology & Pathogenesis

Etiology & Pathogenesis

1

Mycobacteria are slender rods that are acid-fast (i.e., they have a high content of complex lipids that readily bind the **Ziehl-Neelsen stain**)

2

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

3

Transmission usually is direct, by **inhalation of airborne organisms** in aerosols generated by expectoration or by **exposure to contaminated secretions** of infected individual

4

Oropharyngeal and intestinal tuberculosis contracted by drinking milk contaminated with **Mycobacterium bovis** infection (**Primary intestinal TB**)

5

Other mycobacteria, particularly **Mycobacterium avium complex**, they cause disease in 10% to 30% of patients with **AIDS (Atypical mycobacteria)**

The Pathogenesis

Immunity to a tubercular infection is **primarily mediated by TH1 cells**, which stimulate macrophages to kill mycobacteria

This immune response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue destruction.

Defects in any step of TH1 T cell response (including IL-12, IFN- γ , TNF, or nitric oxide production) result in poorly formed granulomas, absence of resistance and disease progression.

Reactivation of the infection or re-exposure to the bacilli in a previously sensitized host results in rapid mobilization of a defensive reaction but also increased tissue necrosis.

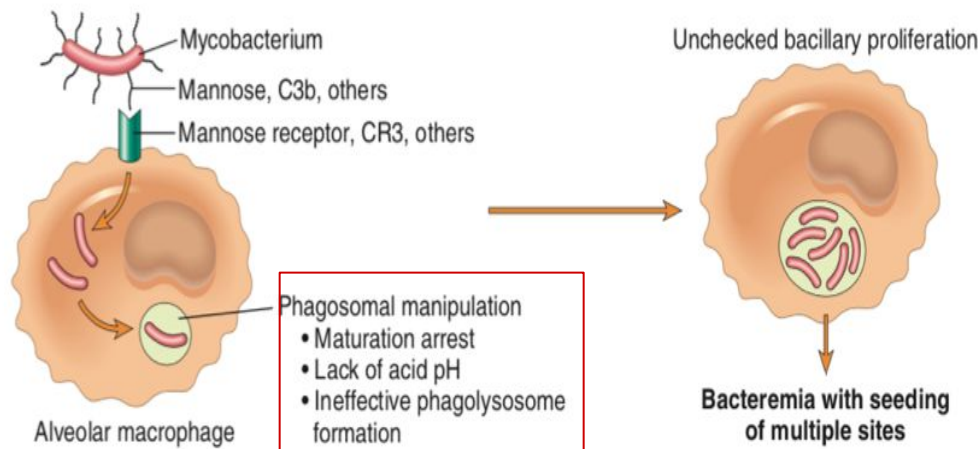
The pathogenesis of Primary TB



[helpful video](#)

- Events occurring in the first 3 weeks after exposure (in non sensitized individual)
- Organism resides in phagosomes of alveolar macrophages

A INFECTION BEFORE ACTIVATION OF CELL MEDIATED IMMUNITY



- The development of resistance to the organism is accompanied by conversion to a positive result on tuberculin skin testing.
- Cells and bacteria are not drawn to scale.

IFN- γ : Interferon γ

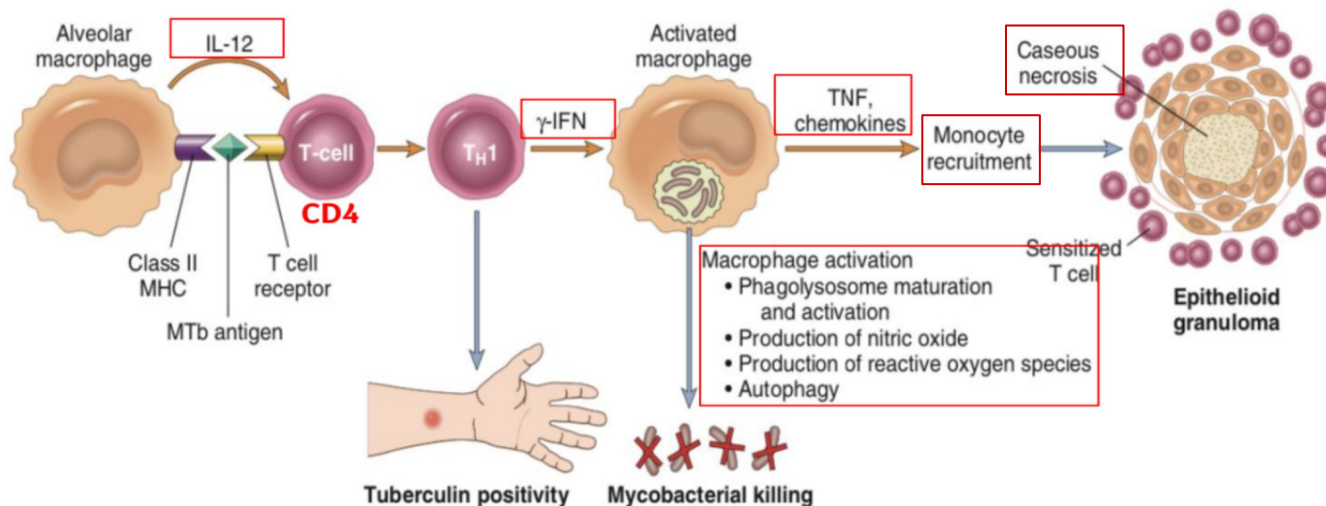
iNOS: inducible nitric oxide synthase

MHC: major histocompatibility complex

MTb : Mycobacterium tuberculosis;

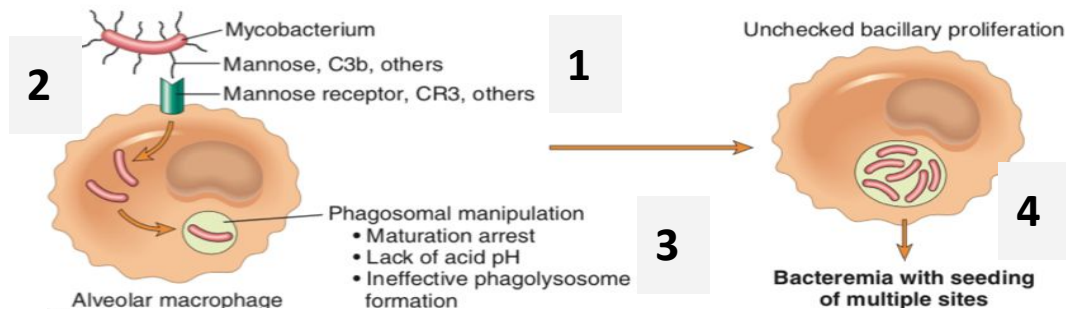
TNF : tumor necrosis factor.

B INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY

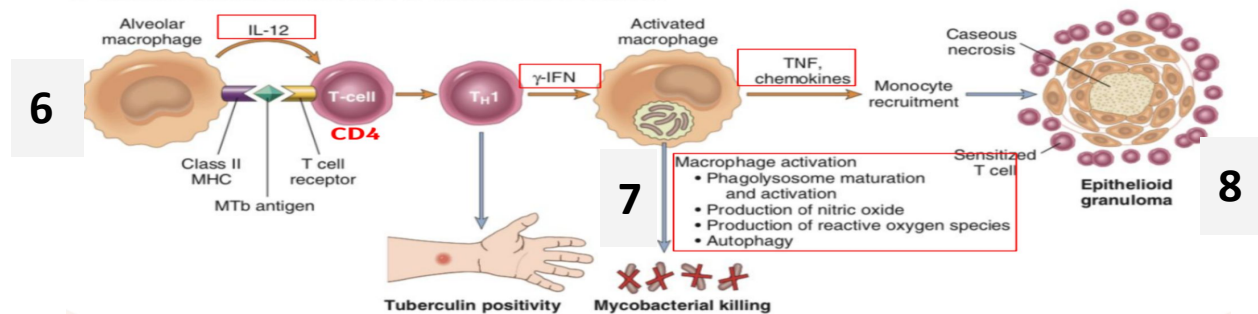


Pathogenesis

A INFECTION BEFORE ACTIVATION OF CELL MEDIATED IMMUNITY



B INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY



1

In the alveolar macrophage there's a receptor called (macrophage mannose receptor) that bind with a molecule present on the surface of the bacteria called mannose capped glycolipid

2

Using the receptor macrophage recognize the bacteria and start phagocytosis

3

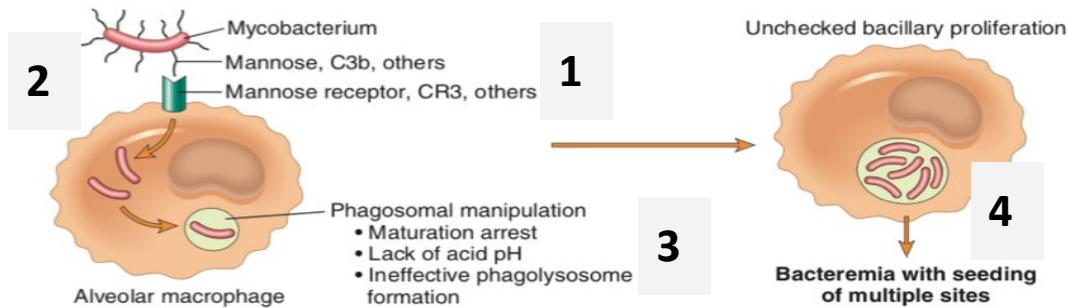
Bacteria then releases (cord factor) that prevent fusion of lysosomes with phagocytic vacuoles

4

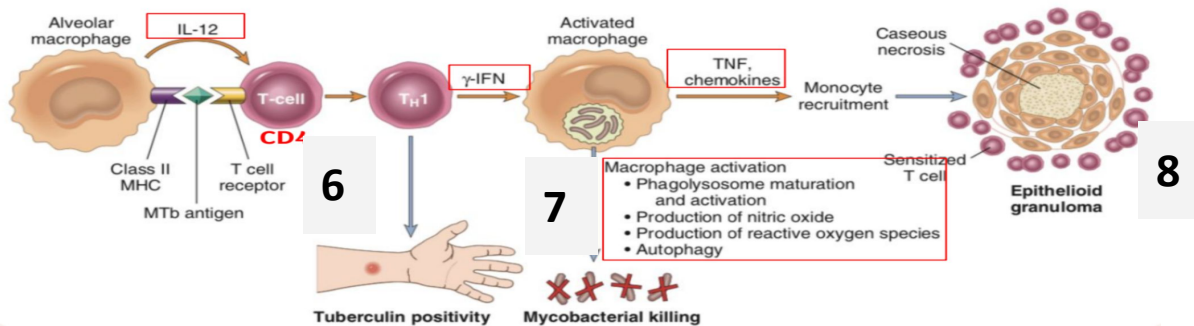
As a result, there's intracytoplasmic proliferation of bacteria within the macrophage

Pathogenesis

A INFECTION BEFORE ACTIVATION OF CELL MEDIATED IMMUNITY



B INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY



5 After 3 weeks , it reaches to the draining lymph nodes

6 The APC presents the antigen through MHC|| to CD4 T cells leading to activation of Th1, As a result of stimulation of Th1, there's areleasing of chemokines and IFN- gamma that activates macrophage

7 Activated macrophages become large and have abundant NO & free radicals, they will also release TNF which will increases the recruitment of monocytes toward the focus of infection..

8 All of that will lead to the formation of a collection of activated macrophages and lymphocytes (Granuloma).

Pathogenesis

1

A molecule on the surface of the bacteria "mannose capped glycolipid." bind to macrophage mannose receptor

2

Bacteria then releases (cord factor) that prevent fusion of lysosomes with phagocytic vacuoles.

3

intracytoplasmic proliferation of bacteria inside the macrophage.

4

The macrophages presents the antigen by MHC II to CD4 T cells leading to activation of Th1

5

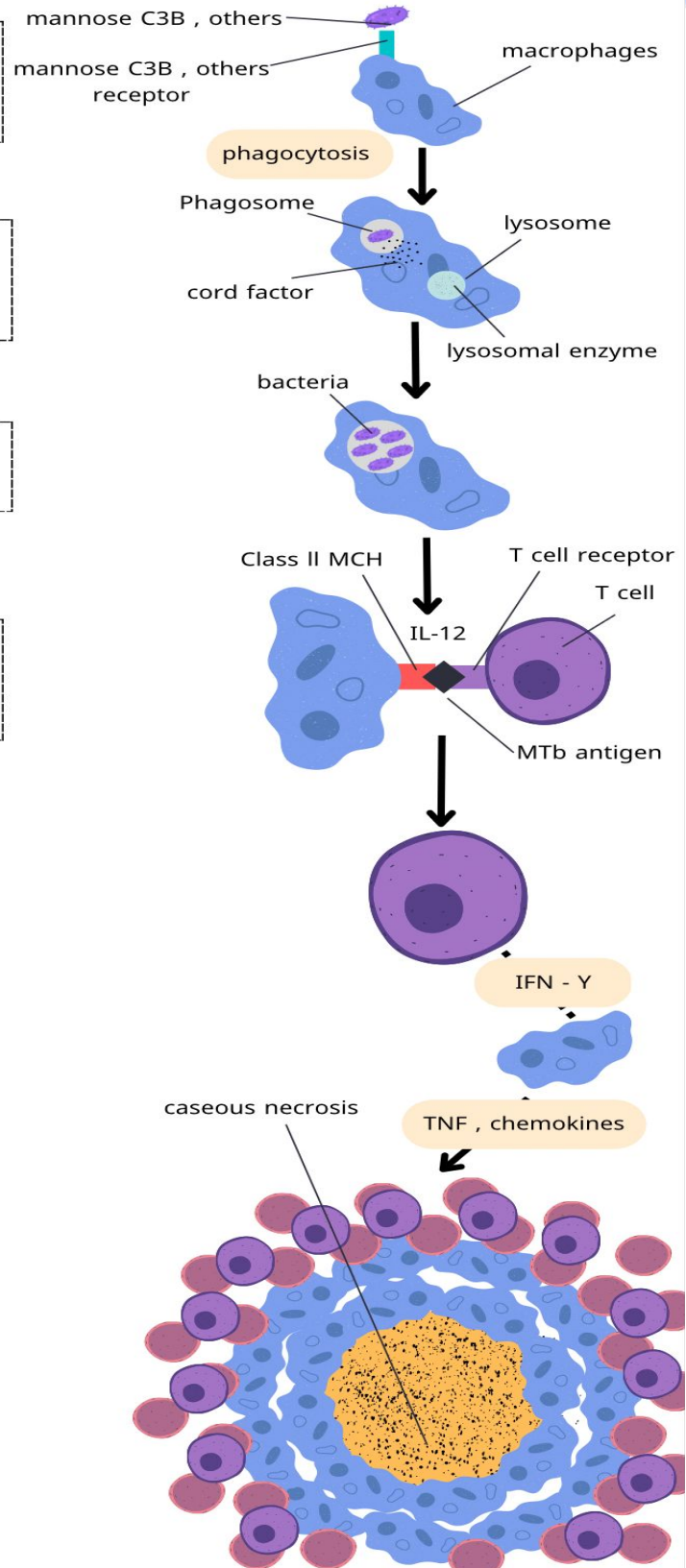
The activated Th1, start releasing of chemokines and IFN-gamma that activates macrophage..

6

Activated macrophages become larger and have release NO & free radicals, besides releasing of TNF which will increase the recruitment of monocytes toward the site of infection

7

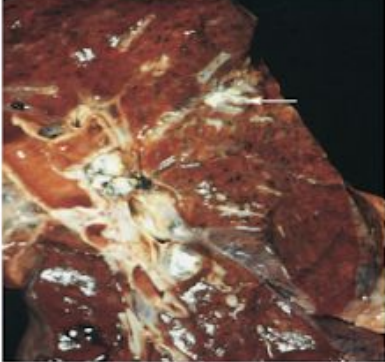

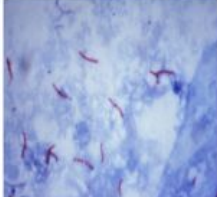
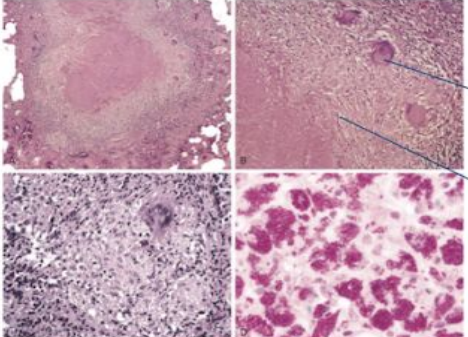
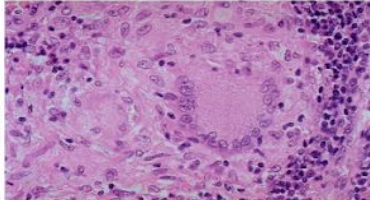
formation of a collection of activated macrophages and lymphocytes (Granuloma).



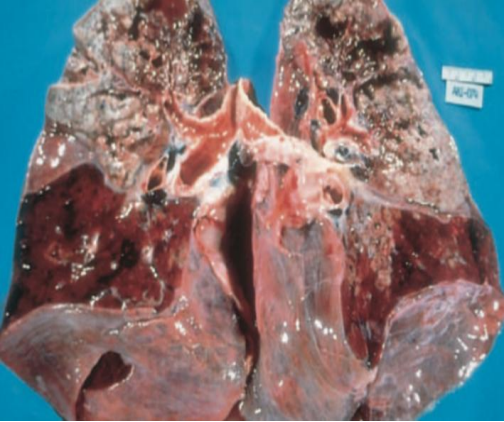
Primary VS Secondary TB

	Primary Tuberculosis	Secondary Tuberculosis
Definition	Form of disease that develops in a previously unexposed and therefore unsensitized patient (1st time exposure). About 5% of those newly infected acquire significant disease.	Pattern of disease that arises in a previously sensitized host (2nd time exposure). It may appear shortly after primary tuberculosis.
Method of infection	inhalation, ingestion	Endogenous due to reactivation of dormant primary lesions many decades after initial infection (specially in immunocompromised individuals or exogenous due to reinfection
Site	lower part of the upper lobe or in the upper part of the lower lobe. (middle or lower lobes)	Apex of lungs or upper part of lower lobe
Characteristic	Ghon focus, Ghon complex	Associated with cavitation
Ability to cause infection	Noninfectious	Highly infectious in +ve patients

Morphology of primary TB

Morphology	Information	Pictures
Ghon complex	<ul style="list-style-type: none"> ● Subpleural location. ● Upper part of the lower lobes or lower part of the upper lobes ● Ghon focus (caseous necrosis) in periphery. ● Ghon complex (caseous necrosis) in hilar lymph nodes. (central area) ● Hilar lymph nodes with caseation. 	
	Gray-white parenchymal focus is under the pleura Hilar lymph nodes with caseation are seen (left).	
organisms	Use of special stains for acid-fast organisms (Ziehl-Neelsen stain) is indicated when granulomas are present (red/pink)	
 <p data-bbox="716 1437 904 1504">Giant cell</p> <p data-bbox="716 1551 904 1618">Histiocyte</p> <p data-bbox="206 1732 707 1780"><small>Fig. 13.15 The morphologic spectrum of tuberculosis. A characteristic tubercle at low magnification (A) and at higher power (B) shows central granulocaseation surrounded by epithelioid and multinucleate giant cells. This is the usual response in individuals who develop cell-mediated immunity to the organism. (C) Occasional case in immunocompetent patients, tubercular granulomas may not show central caseation, hence, irrespective of the presence or absence of caseous necrosis, use of special stains for acid-fast organisms is indicated when granulomas are present. (D) In this specimen from an immunizing guinea pig, sheets of macrophages packed with mycobacteria are seen (pink-blue stain).</small></p>		 <p data-bbox="1155 1589 1505 1608">Microbiology of Tuberculosis / Tuberculous granuloma in lung</p> <p data-bbox="1155 1618 1505 1637">A multinucleated giant cell infiltrate defines the lesion.</p> <p data-bbox="1155 1646 1505 1666">Early central caseation</p>

Secondary pulmonary TB

Information	Pictures
<ul style="list-style-type: none">• The apex of one or both upper lobes are affected with cavitation leading to erosion into and dissemination along airways, patient become infective.	 <p data-bbox="1003 894 1451 942">More tissue destruction</p>

1. Tuberculin test will be converted into +ve after 3 weeks.
 2. The result of stimulation with good immunity = majority of MTB are dead and followed by fibrosis with calcification of ghon focus as healing response (later on ranke complex is gonna develop).
 3. The infected person is asymptomatic or has flu like symptoms.
 4. 90% will have sero+ev (infected)! Test result and only 2-5 cases will develop a disease.
- Pinkish/eosinophilic material = necrosis→used to find the bacilli

Miliary pulmonary disease

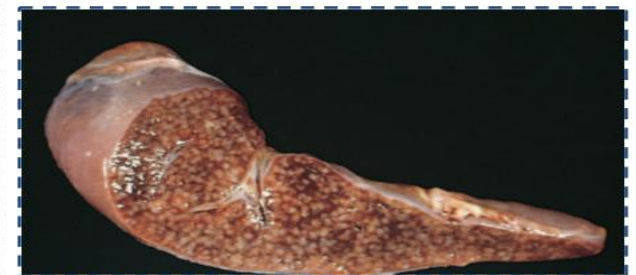
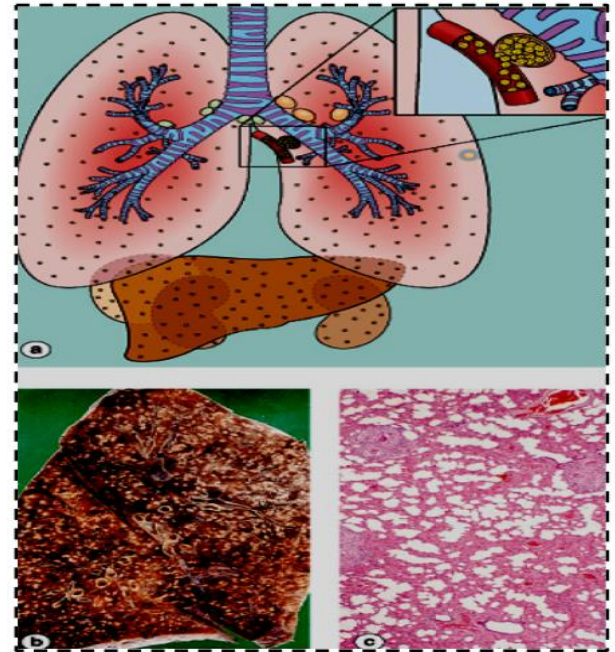
Haematogenous spread of TB organism throughout the body.

When bacteria in the lungs enters the pulmonary venous return to the heart; the organisms subsequently disseminate through the systemic arterial system and the lymphatic channels.

It produces **multiple small yellow nodular lesions** in several organs. Almost every organ in the body may be seeded. Lesions resemble those in the lung.

In the lungs, there multiple lesions either microscopic or small, visible (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma.

note miliary TB can happen in lungs too



Extrapulmonary tuberculosis

1

Lymph nodes (tuberculous lymphadenitis): are the most frequent form of extra pulmonary tuberculosis esp. in the cervical region

2

Pleura with effusion (exudate) cause granulomatus hepatitis

3

Liver and spleen

4

Adrenals cause 2nd Addison's disease -> hypocortisolism

5

Kidneys

6

Epididymis and prostate cause epididymitis -> infertility

7

Fallopian tube and endometrium cause salpingitis -> infertility

8

Meninges around the base of the brain (**tuberculous meningitis**)

9

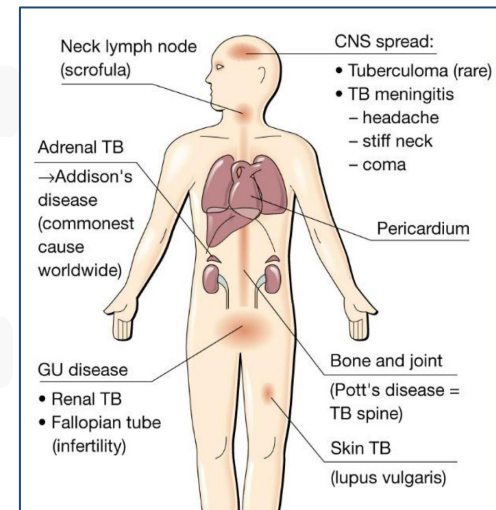
Bone marrow cause leukoerthroblastosis

10

Vertebrae (**Pott's disease**)

9

intestinal tuberculosis

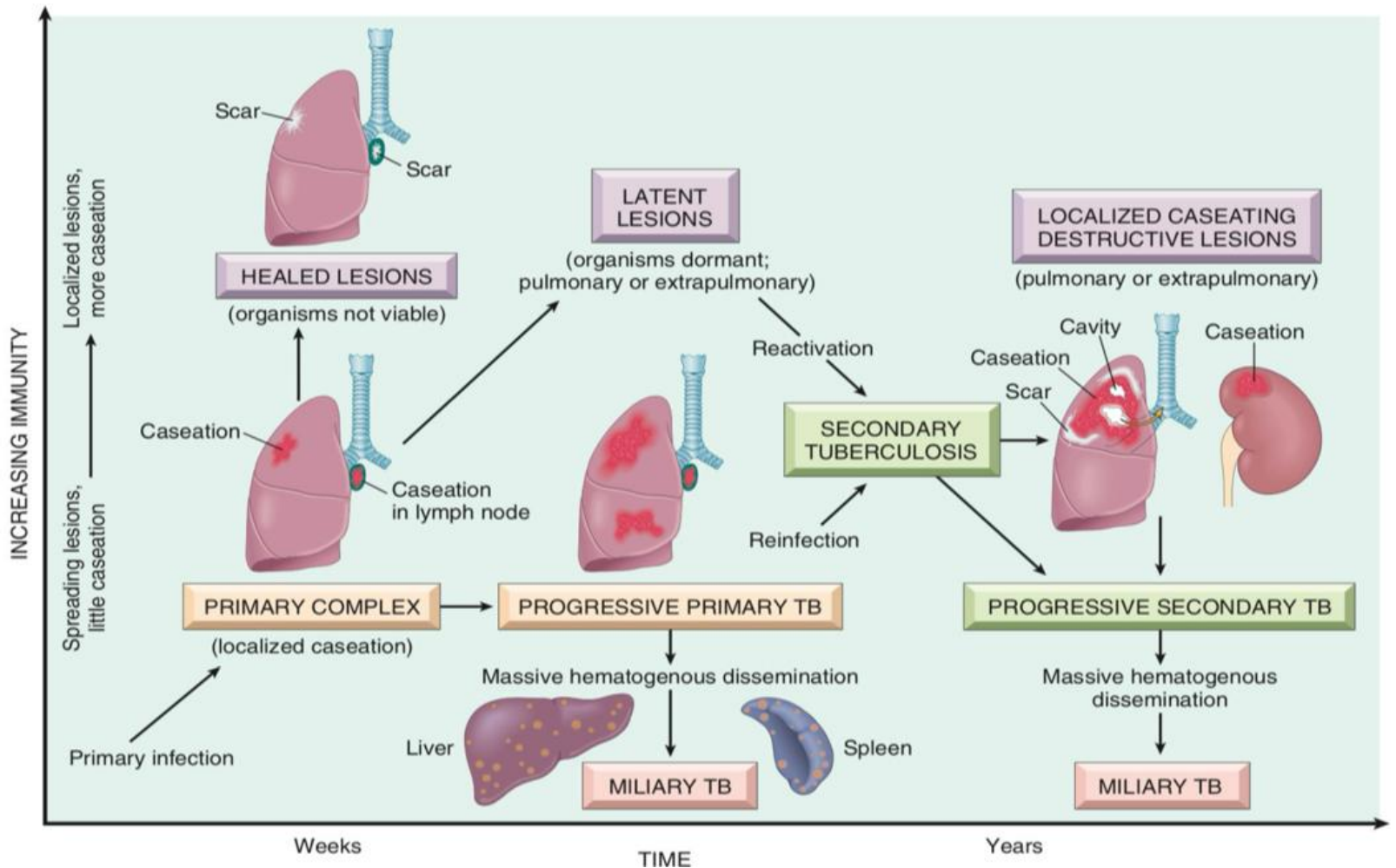


Pott's disease



Vertebrae (pott's disease). It collapses the spine and leads to paraspinal "cold" abscess. (Compressed scoliosis)

In these patients, infected material may track along tissue planes to present as an abdominal or pelvic mass .



Clinical features

Clinical features

General

Malaise

anorexia

weight loss

Fever

low grade

night sweating

Cough

Hemoptysis

is present in about half of all cases of pulmonary tuberculosis.

May be asymptomatic (can occur in primary TB even with bacteremia)

Depend on the organ system involved (e.g. tuberculous salpingitis may present as infertility, tuberculous meningitis with headache and neurologic deficits, pott disease with back pain and paraplegia). If it disseminates→other symptoms will occur e.g.intestinal TB→abdominal pain, vomiting

Diagnosis of T.B

Based on the history ,physical and radiographic findings of consolidation or cavitation in the apices of the lungs.

Ultimately, tubercle bacilli must be identified by

Radiology

Ziehl-Neelsen stain

Mantoux skin test

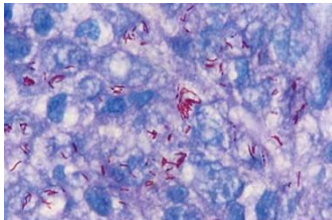
Culture

PCR

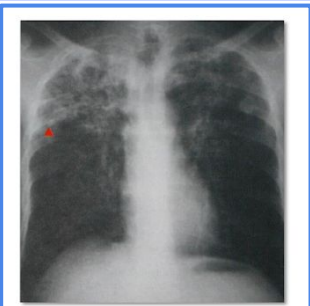
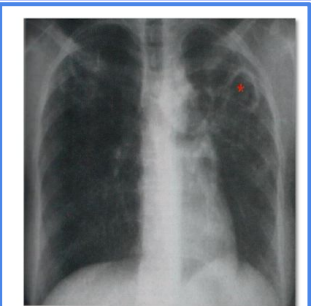
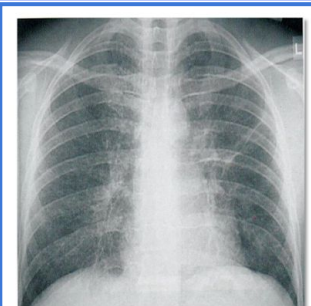
the organism stains red/pink.

remains the gold standard.

amplification of M. tuberculosis DNA allows for rapid diagnosis



Ziehl-Neelsen stain shows red acid-fast staining M.tubercular bacilli

			Male slide
Both upper lobes are affected	Cavity formation	Miliary tuberculosis	
			

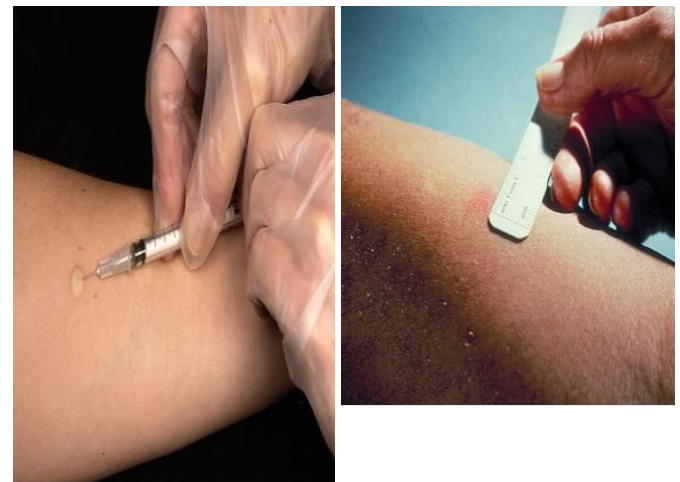
Mantoux skin test

Female doctor didn't focus on this

Definition

- A positive tuberculin skin test result signifies cell-mediated hypersensitivity to tubercular antigens, but doesn't differentiate between infection and disease.
- The size of induration is measured 48–72 hours later
- Positive results: induces a visible and palpable induration (at least 5 mm in diameter)

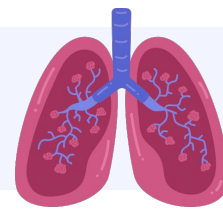
False-negative	False-positive
reactions may be produced by certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression and AIDS.	reactions may result from infection by atypical mycobacteria
Means the patient has the disease but the test is negative	Means the patient doesn't have the disease but the test is positive



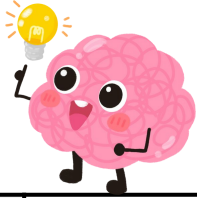
Prognosis

- 1** The prognosis with proper treatment is generally good if infections are localized to the lungs.
- 2** When they are caused by drug-resistant strains or occur in aged debilitated, or immunosuppressed persons, who are at high risk for developing miliary TB.
- 3** The outcome depends on the adequacy of the host immune response and treatment.

Summary



- Tuberculosis is a chronic granulomatous disease caused by *M. tuberculosis*, usually affecting the lungs.
- Initial exposure to mycobacteria results in development of a cellular immune response that confers resistance and leads to hypersensitivity.
- The TH1 subset of CD4+ T cells has a crucial role in cell-mediated immunity against mycobacteria.
- The histopathologic hallmark of host reaction to tuberculosis in immunocompetent individuals is the presence of granulomas, usually with caseous necrosis.
- Primary pulmonary tuberculosis in immunocompetent individuals is asymptomatic and results only in healed lesions, typically in a sub-pleural focus and a draining lymph node.
- Secondary (reactivation) tuberculosis arises in previously exposed individuals when host immune defenses are compromised, and usually manifests as cavitary lesions in the lung apices.
- Both progressive primary tuberculosis and secondary tuberculosis can result in systemic seeding, causing life-threatening forms of disease such as miliary tuberculosis and tuberculous meningitis.
- HIV-seropositive status is an important risk factor for development or recrudescence of active tuberculosis



KEYWORDS

TB	<ul style="list-style-type: none">•Fever, Night sweat (very important),Hemoptysis,Weight loss,Associated with Silicosis•Interferon gamma release assay (IGRA) + PPD-> tests for latent TB, but IGRA is more specific• tuberculin test(PPD)(Mantoux), skin cell mediated immunity•Granular necrosis
Miliary	weight loss,fever ,productive blood-stain cough and night sweats chest x-ray showed numerous small nodules in both lungs. (can present as meningitis or vertebral osteomyelitis (POTTs))
IFN- γ	used to diagnose latent TB secreted by Th1 useful predicting the development of tuberculosis
hematogenous	the way that miliary TB spread throughout the body
IL-12	In TB is secreted by macrophages and change CD4T to TH1
Tuberculin test	Redness and induration after 72 hours.

Answers:

1-B 2-B 3-D 4-A 5-D

6-A 7-B 8-C



MCQ

1- Which type of TB is associated with cavitation			
A)Primary	B)Secondary	C)Both	D)None of them
2- The macrophages can recognize M.tuberculosis by			
A)FAS receptor	B)Mannose receptor	C)Intracellular receptor	D)None of them
3-Method of infection of Primary tuberculosis			
A)Inhalation	B)Ingestion	C)Endogenous	D)A & B
4- 20-year-old man from China is evaluated for persistent cough, night sweats, low-grade fever, and general malaise. A chest X- ray reveals findings “consistent with a Ghon complex.” Sputum cultures grow acid-fast bacilli. Examination of hilar lymph nodes in this patient would most likely demonstrate which of the following pathologic changes?			
A)caseous necrosis	B)fat necrosis	C)Fibrinoid necrosis	D)Liquefactive necrosis
5- GHON focus is generally located in:			
A)upper part of the lower lobe.	B)lower part of the upper lobe.	C)upper part of upper lobe.	D)A and B
6-Oropharyngeal and intestinal tuberculosis contract by drinking milk contaminated with			
A)bovis infection	B)Mycobacterium avium	C)Mycobacterium	D)Africanum
7-TB is diagnosed by			
A)Gram stain	B)Ziehl-Neelsen (AFB) stain	C)Masson trichromatic	D)A&C
8- IL-12 is secreted by which cell of the following:			
A)Neutrophils	B)TH2	C)Activated macrophages	D)TH1

YOU CAN DO IT Cases

1-A 21-year old male came to the chest clinic with a history of weight loss, fever, productive blood-stain cough and night sweats. Chest X-ray showed some small yellow nodules in both lungs, what type of TB does this patient have?

A)primary

B)secondary

C)Miliary

D) Localized

2- -A biopsy from the cervical lymph nodes of a patient with constitutional symptoms reveals caseating granulomas. What is the most likely diagnosis?

A) Interstitial lung disease

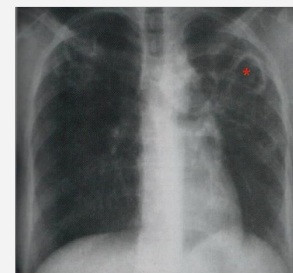
B) Lung cancer

C)Tuberculosis

D)Sarcoidosis

3- A 60-year-old man presents with a history of productive cough for 5 months. The cough has not improved with inhaled beta agonists. The patient experienced Hemoptysis and lost 10lb in the last week, he also complained from night fever that decrease in the morning, , x-Ray showed the following: :

he most likely have



A)primary TB

B)secondary TB

C)Pneumonia

D)COPD

4- A 32-year-old male presents to his corporate health office prior to starting a new job as a perfusion technologist. As part of the onboarding process, he receives screening for tuberculosis using a Mantoux skin test (also termed purified protein derivative test). The patient inquires about how the Mantoux skin test results will be interpreted. Which of the following is most suggestive of a positive test?

Extra question

A) Induration of 1 mm in an HIV positive patient

B)Induration of 5 mm in a patient with IV drug use

C) Induration of 15 mm in an otherwise healthy patient

D) Induration of 5 mm in a patient who immigrated from Mexico ten years ago

5-A 46-year-old female presents to the emergency department with complaints of fever, cough, and night sweats over the past 2-3 months. Past medical history is notable for HIV infection, type II diabetes mellitus and hypertension. She is currently undomiciled, drinks 3-4 alcoholic drinks per day, smokes one pack of cigarettes per day, and uses intravenous heroin daily. Temperature is 37.2 °C (99.0°F), pulse is 87/min, respirations are 16/min, blood pressure is 156/74 mmHg, and O₂ saturation is 95% on room air. Physical exam demonstrates a thin, cachectic middle aged female with track marks noted on the upper extremities bilaterally. Cardiopulmonary exam reveals rales in the upper lobe of the left lung, without gallops, rubs, or murmurs.

Chest x-ray is demonstrated below.

Which of the following is the most important contributing factor for the development of this radiographic finding?



A) Embolization of bacterial vegetations

B) Increased lymphatic drainage

C) Higher oxygen tension in upper lung lobes

D) Inhibition of opsonization

6- A 57-year-old female presents to the emergency department with a worsening cough, shortness of breath, and night sweats. In addition, the patient has experienced a 10 lb weight loss over the past 2 months despite having made no changes to her diet. She was recently released from incarceration and smokes one pack of cigarettes per day. Past medical history is notable for hypertension and hyperlipidemia. The patient was born in Mexico and had a positive PPD test as an adolescent. Chest x-ray is demonstrated below:

Which of the following best describes the radiographic finding?



A) Fibrocavitary lesion in the upper lobes

B) Primary focus of mycobacterial infection

C) Cavitary caseating lesion

D) Calcified mycobacterial lesion and ipsilateral calcified hilar lymph nodes

Pathology team

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