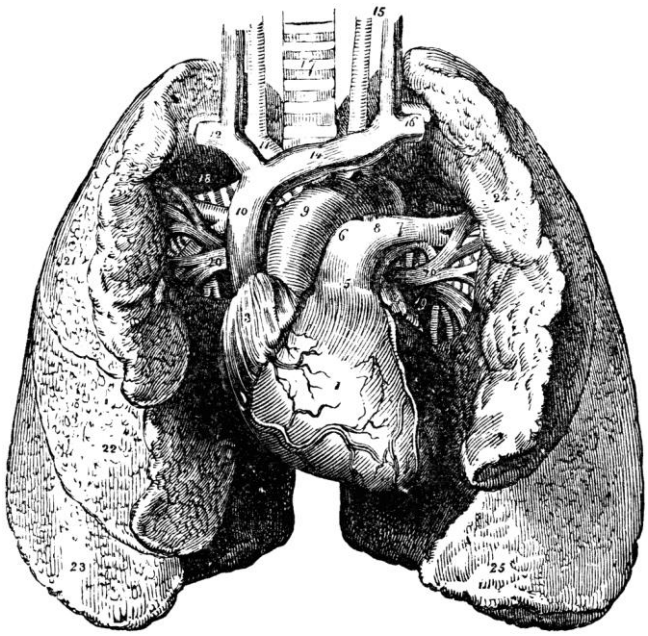


Pathology
teamwork

Lecture (3): TUBERCUOSIS

Color Index :–

- **VERY IMPORTANT**
- Extra explanation
- **Examples**
- **Diseases names: Underlined**
- **Definitions**

*وإن الطِّبَّ مهنةُ كُلِّ حُرٍّ، رأى أن يَبذلَ الجهدَ اجتهادا

OBJECTIVES:

- **Define tuberculosis.**
- **List the diseases caused by mycobacteria.**
- **Know the epidemiology of tuberculosis (tb).**
- **List conditions associated with increased risk of tuberculosis.**
- **List factors predisposing to extension of the infection.**
- **Recognize the morphology of mycobacteria and its special stain (the ziehl-neelsen) as well as the morphology of granulomas in tb (tubercles).**
- **Know the pathogenesis of tuberculosis**
- **In regards to mycobacterial lung infection: compare and contrast the following in relation to their gross and histologic lung pathology:**
  - Primary tuberculosis (include a definition of the ghon complex).
  - Secondary or reactivation tuberculosis.
  - Miliary tuberculosis.
- **List organs other than lung that are commonly affected by tuberculosis.**
- **Know the basis and use of tuberculin skin (mantoux) test.**
- **List the common clinical presentation of tuberculosis.**
- **List the complication and prognosis of tuberculosis.**

TUBERCUOSIS

- **Tuberculosis: is a serious chronic granulomatous pulmonary and systemic disease caused most often by *M. tuberculosis*.**

Diseases Caused By Mycobacteria

➢*Mycobacterium tuberculosis* is the etiologic agent of Tuberculosis in humans. Humans are the only reservoir for the bacterium.

➢*Mycobacterium bovis* is the etiologic agent of TB in cows and rarely in humans. Both cows and humans can serve as reservoirs. Humans can also be infected by the consumption of unpasteurized milk. This route of transmission can lead to the development of extrapulmonary TB.

➢*M. leprae*: causes leprosy

Others:

➢*M. kansasii, M. avium,* and *M. intracellulare* cause atypical mycobacterial infections in humans especially in AIDS. They cause respiratory and gastrointestinal symptoms and can involve other organs too.

➢*M. ulcerans* causes Buruli ulcers of skin.

Epidemiology Of Tuberculosis:

- According to the World Health Organization (WHO), tuberculosis is estimated to affect more than a billion individuals worldwide, with 8.7 million new cases and 1.4 million deaths each year.

Factors predisposing to extension of the infection, flourishes wherever there is:

1. Poverty
2. Crowding
3. Malnutrition
4. Chronic debilitating illness e.g. Chronic lung disease (particularly silicosis), chronic renal failure etc.

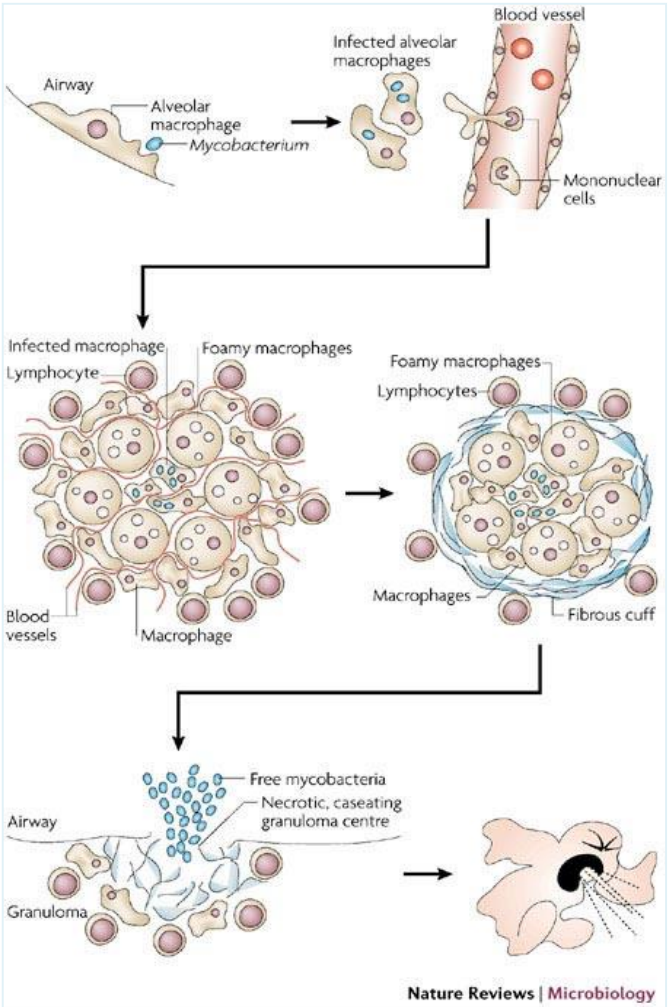
Conditions associated with increased risk of tuberculosis:

- A disease of the elderly (old people are more prone to infection)
- People with AIDS
- Diabetes mellitus
- Hodgkin's lymphoma
- Alcoholism
- Chronic lung disease (particularly silicosis)
- Immunosuppression e.g. with glucocorticoids

GRANULOMA

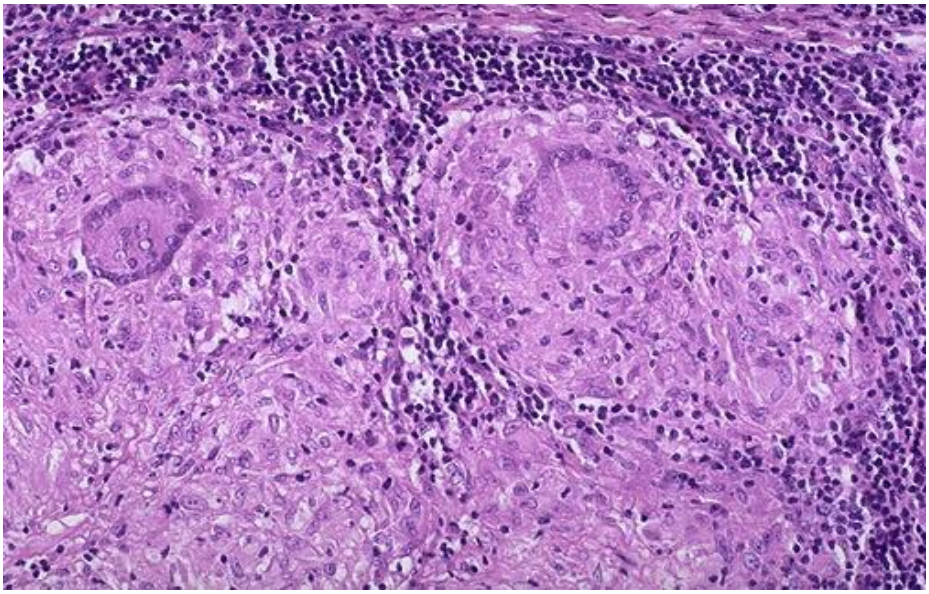
- Tuberculosis is a granulomatous disease.
- A granuloma is a microscopic aggregation of macrophages that are transformed into epithelium-like cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.
- Epithelioid cells fuse to form giant cells containing 20 or more nuclei.
- The nuclei are arranged either peripherally (Langhans-type giant cell) or haphazardly (foreign body-type giant cell). Both Langhans ("Classic TB") and foreign-body giant cells are common.
- These giant cells can be found either at the periphery or the center of the granuloma.
- Fibrous connective tissue often surrounds granulomas (remodeling of tissue).
- In TB Areas within the granuloma can undergo necrosis (caseous necrosis). Necrosis can lead to calcification.
- TB granulomas are called tubercles, and if they are caseating in the center, they are called soft tubercles.

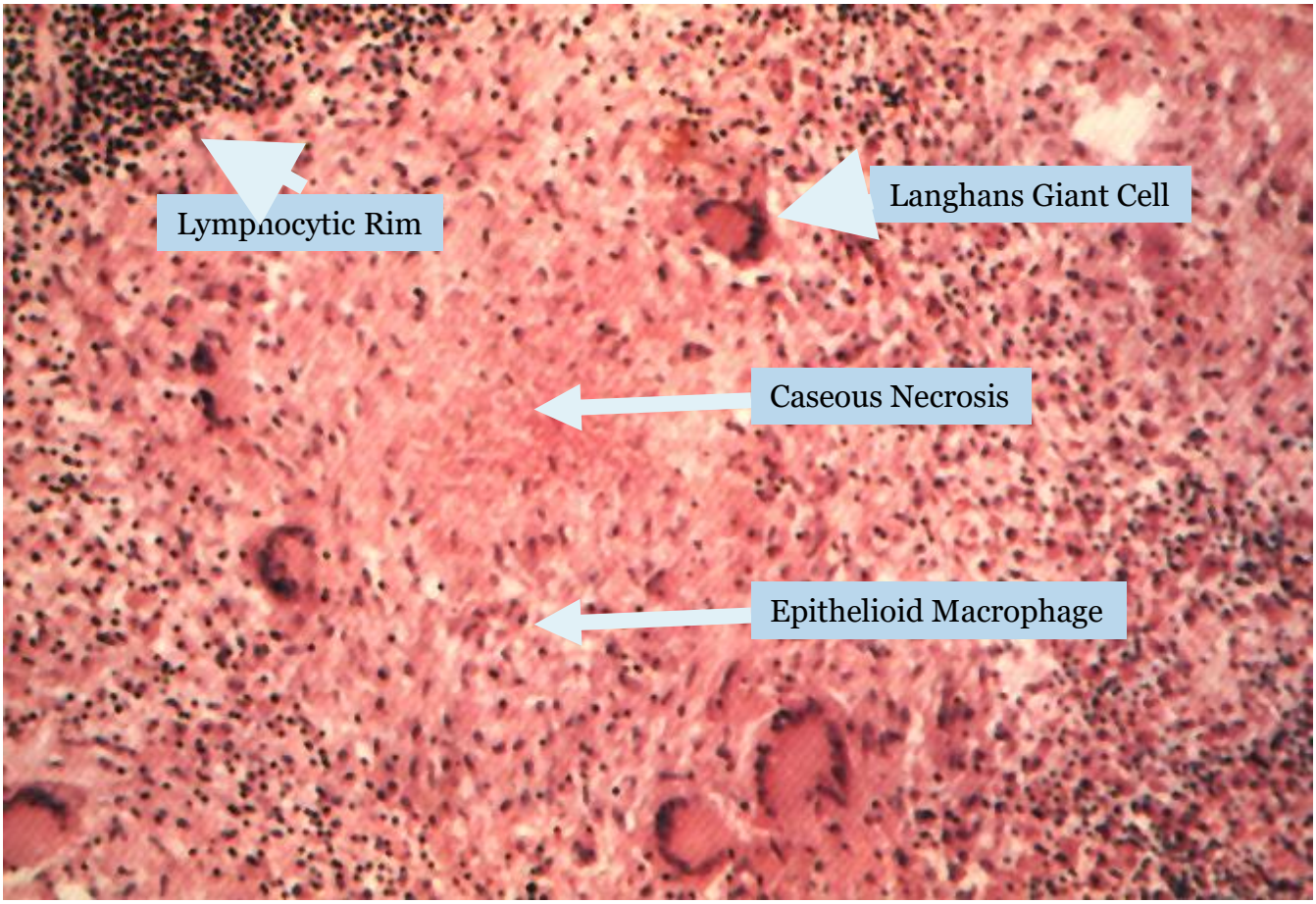
Morphology Of Granulomas In TB (Tubercles):

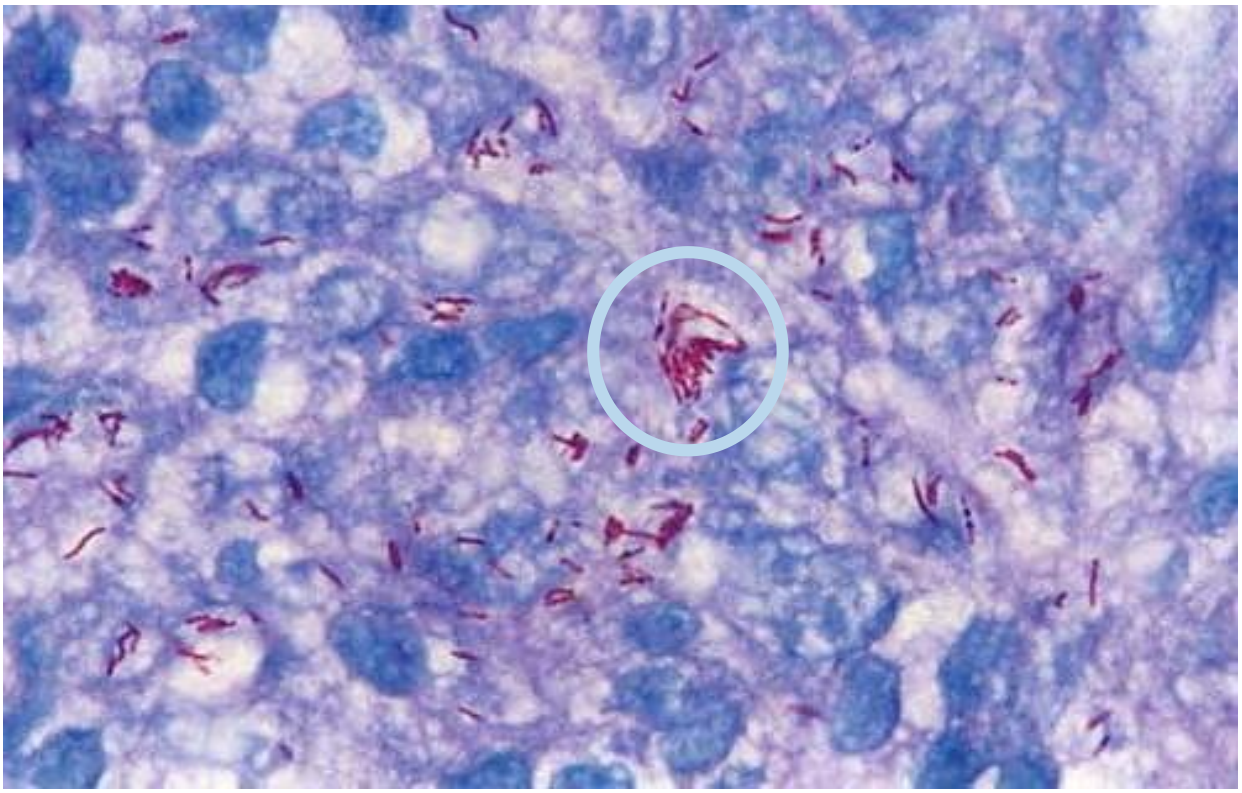


MORPHOLOGY OF GRANULOMAS IN TB (TUBERCLES) CONTINUED

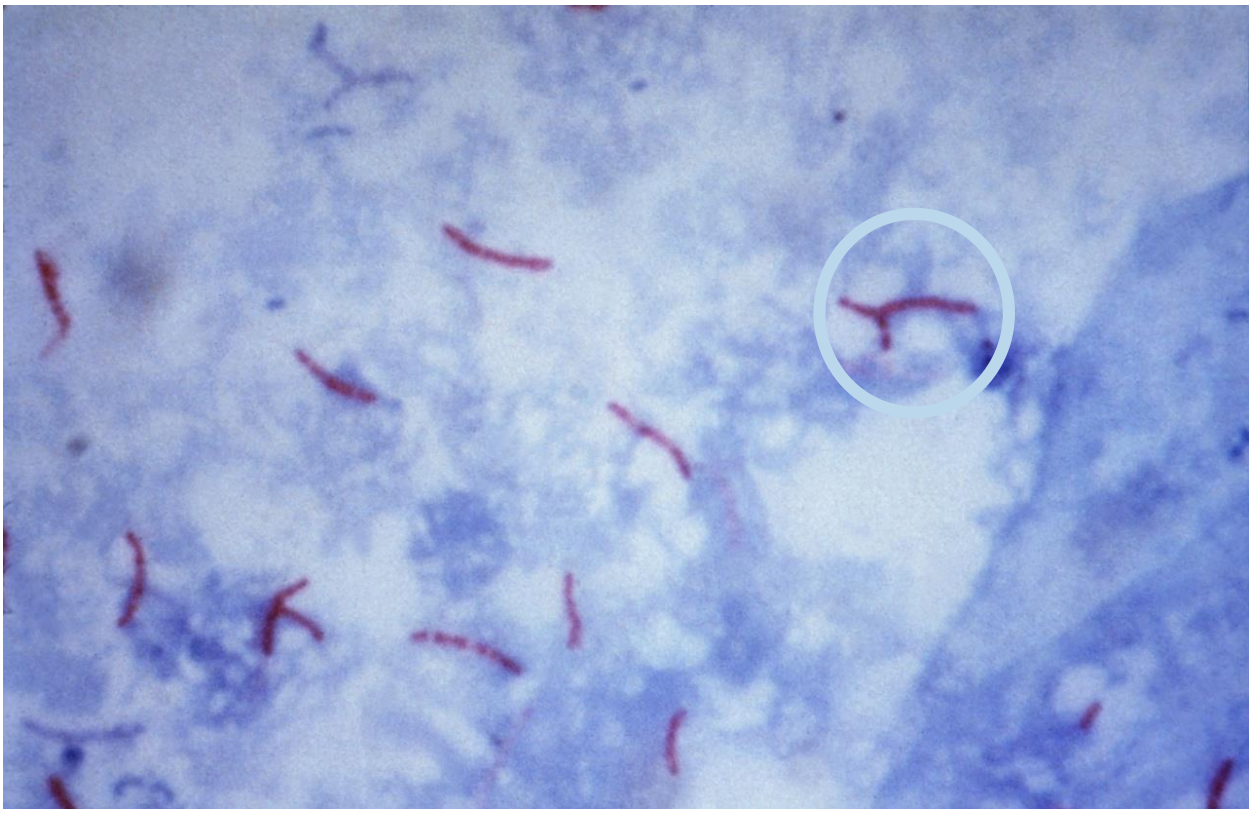
- Granuloma: the predominant cell type is an activated macrophage with a modified epithelial-like (epithelioid) appearance. Also seen are lymphocytes, multinucleated giant cells and occasional plasma cells.







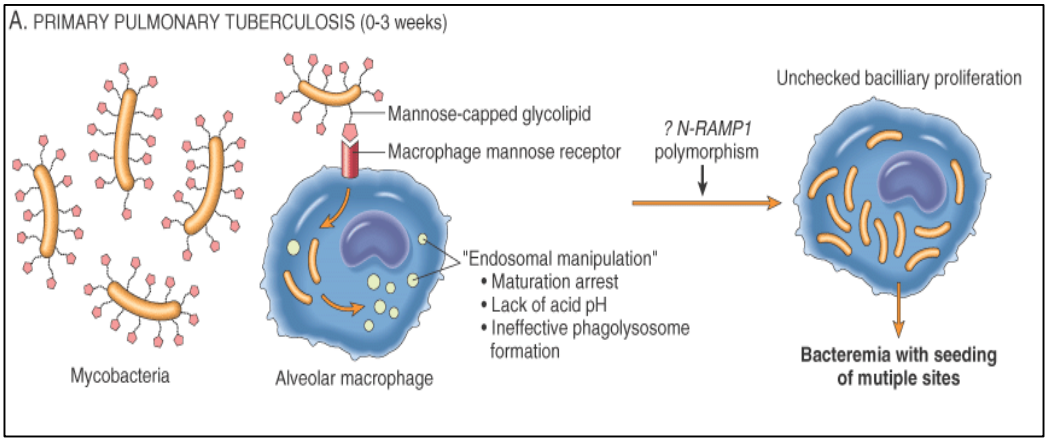
- Ziehl-Neelsen stain is an acid-fast staining method to stain *M. tuberculosis*. The Acid-fast bacilli appear pink in a contrasting background (Methylene Blue of Brilliant Green).



PATHOGENESIS OF TUBERCULOSIS

The steps in M. tuberculosis infection are :

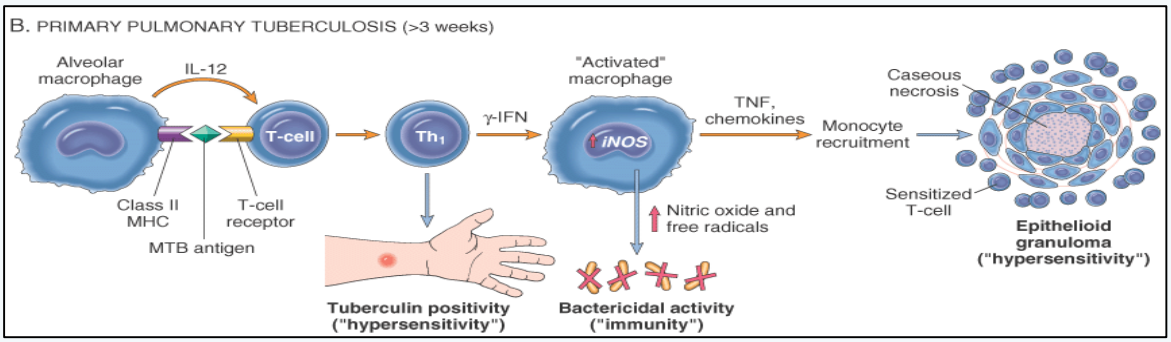
1. ***Entry into macrophages:*** Phagocytosis mediated by several receptors expressed on the phagocyte, including mannose binding lectin	**2.** ***Replication in macrophages.*** *M. tuberculosis* inhibits maturation of the phagosome and blocks formation of the phagolysosome (by inhibiting Ca^{2+} signals), allowing the bacterium to replicate within the vesicle, protected from the microbicidal mechanisms of lysosomes .



During the earliest stage of primary tuberculosis (<3 weeks) in the no sensitized individual, bacteria proliferate in the pulmonary alveolar macrophages and air spaces, resulting in bacteremia and seeding of multiple sites. Despite the bacteremia, most people at this stage are asymptomatic or have a mild flu-like illness

PATHOGENESIS OF TUBERCULOSIS

3. ***The T_H1 response.*** About 3 weeks after infection, a T-helper 1 (T_H1) response is mounted that activates macrophages, enabling them to become bactericidal. (at this point when a person is sensitized with Th1, they test positive in the tuberculin test)



Differentiation of T_H1 cells depends on IL-12, which is produced by antigen-presenting cells that have encountered the bacilli

TH1-mediated macrophage activation and killing of bacteria by produce IFN-γ

Macrophages activated by IFN-γ differentiate into the "epithelioid histiocytes" that aggregate to form granulomas

4. ***T_H1-mediated macrophage activation and killing of bacteria*.**

IFN-γ is the critical mediator that enables macrophages to contain the *M. tuberculosis* infection. How?

1. IFN-γ stimulates maturation of the phagolysosome in infected macrophages, exposing the bacteria to a lethal acidic, oxidizing environment.
2. IFN-γ stimulates expression of inducible nitric oxide synthase, which produces nitric oxide (NO)
3. IFN-γ mobilizes antimicrobial peptides (defensins) against the bacteria
4. IFN-γ stimulates autophagy, a process that sequesters and then destroys damaged organelles and intracellular bacteria such as *M. tuberculosis*.

PATHOGENESIS OF TUBERCULOSIS

5. ***Granulomatous inflammation and tissue damage.***

Macrophages activated by IFN-γ differentiate into the "epithelioid histiocytes" that aggregate to form granulomas; some epithelioid cells may fuse to form giant cells (langhans giant cell).
Activated macrophages also secrete TNF and chemokines, which promote recruitment of more monocytes

Role of other immune cells: In addition to the T_H1 response, NKT cells that recognize mycobacterial lipid antigens bound to CD1 on antigen-presenting cells, or T cells that express a γδ T-cell receptor, also make IFN-γ.

PATHOGENESIS OF GRANULOMA

Pathogenesis of granuloma

Host susceptibility to disease. People with genetic deficiencies in the IL-12 pathway and the IFN-γ pathway, including STAT1 a signal transducer for IFN-γ, are vulnerable to severe mycobacterial infections.

Polymorphisms in a large number of genes, including HLA, IFN-γ, IFN-γ receptor, and TLR2 have been found to be associated with susceptibility to tuberculosis.

SUMMARY OF PATHOGENESIS

- Immunity to *M. tuberculosis* is primarily mediated by T_H1 cells, which stimulate macrophages to kill the bacteria
- This immune response, while largely effective, comes at the cost of accompanying tissue destruction
- 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
- loss of T-cell immunity (indicated by tuberculin negativity in a previously tuberculin-positive individual) may be an ominous sign that resistance to the organism has faded

ROUTE OF TRANSMISSION OF TB

- M. bovis infections, acquired through drinking infected milk, usually start in the tonsils or Peyer's patches.

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

WHEN THE BACILLI ENTERS THE BODY:

The bacilli have 5 potential fates upon entering the human body:

1- They may be killed by the immune system

2- They may multiply and cause primary TB

3- They may become dormant and remain asymptomatic

4- They may proliferate after a latency period (reactivation disease). Reactivation TB may occur following either (2) or (3) above.

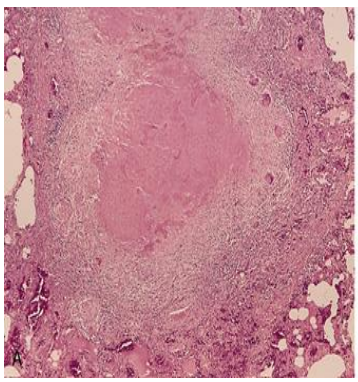
5- If immunosuppressed - Primary Progressive TB or Miliary TB

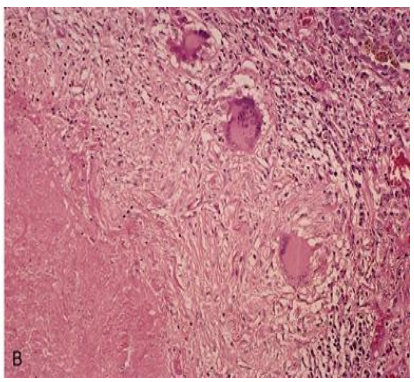
The clinical course or presentation of TB:

- The course of TB depends on the **age** and the **immunity of the patient** and **the total burden of organism**.
- Some patients have only an indolent, **asymptomatic infection** while in others TB is a **destructive disseminated disease**.
- There is a difference between infection and active TB. Not everyone who is infected develops clinical symptoms.
  - **a. Primary TB occurs on first exposure to the organism and can pursue either an indolent or aggressive course (primary progressive TB).**
  - **b. Secondary TB develops long after a primary infection, mostly as a result of reactivation of a primary infection. It can also be produced by exposure to exogenous organisms. Secondary TB is always an active disease.**
  - **c. Miliary TB**

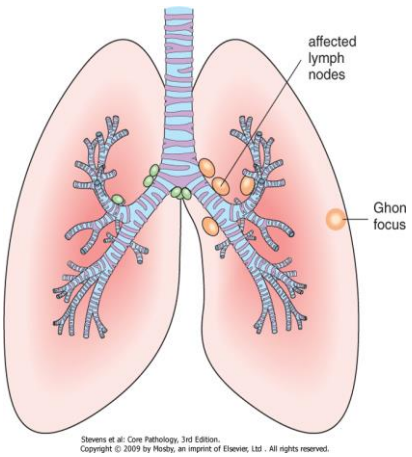
PRIMARY TB:

- Primary TB is a first exposure to tubercle bacilli. The inhaled organism is deposited in the alveoli.
  - Ingested by macrophages and they elicit a **type IV delayed hypersensitivity response**
  - In a immunologically competent person a granulomatous response in produced. It takes 5-6 days invoke granuloma formation which are usually formed by 3 to 4 weeks.
- In immunocompromised persons, granulomas are poorly formed.
- The lung lesion of primary TB is known as **Ghon focus**.
- It is commonly found in the **sub-pleural area.**
- It drains into **the hilar lymph nodes.**
- The combination of the **Ghon focus** and the involved **mediastinal or hilar lymph** nodes is called as **Ghon complex.**
- Most of the time this Ghon complex heals undergoing **shrinkage fibrous scarring and calcification. It takes 2 to 8 weeks for healing.**
- **Clinically**: low grade fever and flu like symptoms
- Chest x-ray shows a subpleural midzonal round lesion with hilar lymph nodes enlargement.
- Tuberculin **skin test become positive.**



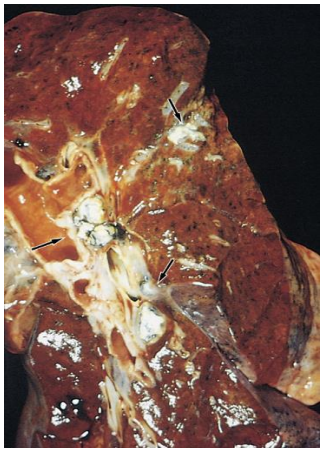


Caseating granulomas



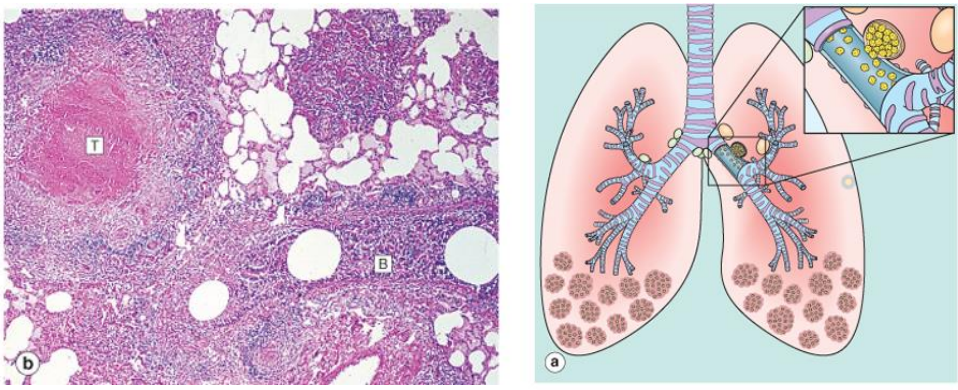
POSSIBLE SEQUALAE OF PRIMARY TUBERCULOSIS

PRIMARY TUBERCULOSIS: Ghon Focus & Ghon complex:



- Ghon Focus: lung lesion of primary TB, involves upper segments of the lower lobes or lower segment of the upper lobe.
- Ghon complex: combination of a peripheral Ghon focus and involved mediastinal or hilar lymph node.
- Microscopically the classic lesion of TB is a caseous granuloma.

- **No problems**.
- The disease may advance into **progressive primary tuberculosis** in immunocompromised patients such as AIDS patients, elderly, and malnourished children. The infection progresses and spreads to other areas of lung, lymph nodes or other multiple sites.
- The foci of scarring may harbor a small number of organisms that remain viable for years and later if immune mechanisms wane or fail, these bacilli may multiply and cause reactivation of TB (**secondary TB**).



progressive primary tuberculosis

SECONDARY TUBERCULOSIS

It is post primary infection in an immunized individual.

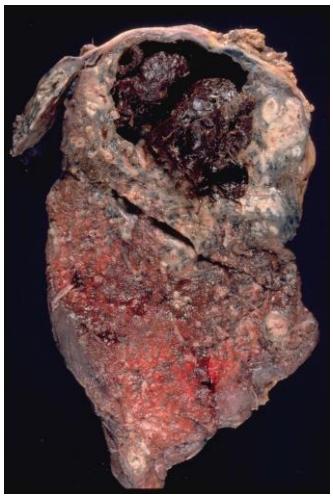
The mycobacteria in secondary TB may be either coming from:

1) A reactivation of dormant organisms from old granulomas (**dormant primary lesion).**
   - ❖ This is more common.
   - ❖ It may develop even decades after primary infection.
   - ❖ Causes: vvarious conditions including:
     - I. Cancer
     - II. Chemotherapy
     - III. AIDS
     - IV. Old age
2) Exogenous re-infection **(newly acquired bacilli)** by a high dose of virulent bacilli.
   - Seen more in endemic areas.

Pathologic features of secondary tuberculosis:

- **Secondary pulmonary tuberculosis can involve any organ but the lungs are the most common site.**
  - In the lungs it is classically localized to the **apex** of the **upper lobes** of one or both lungs.
    - ➢ (M. Tuberculosis bacilli love oxygen and prefer to grow where it is most abundant so it starts at the apical and subapical regions of the lungs).
  - Appear grossly as sharply circumscribed firm mass with **central cavity surrounded by fibrous wall.**
  - The **cavitation** is loaded with the mycobacteria. It becomes an important source of infection because the patient now coughs sputum that contains bacilli.
  - **Histologically:** epithelioid granulomas with central caseation and Langhan's type.

Secondary TB – Lungs:



Cavitatory tuberculosis with intracavitary hemorrhage.

Extensive necrosis with cavitation, usually occurring in the upper lung lobe.

Complications of TB:

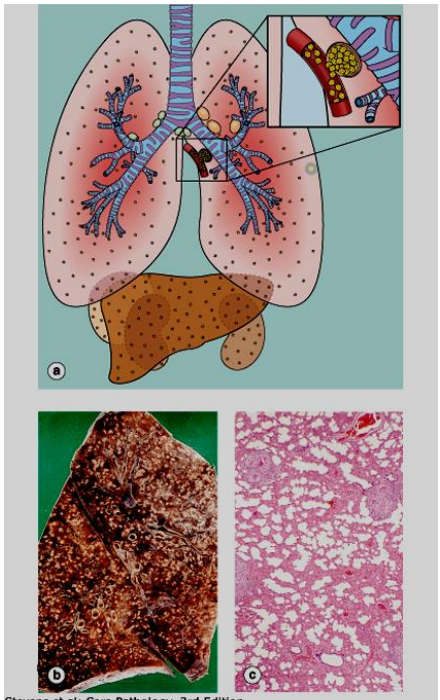
- Scarring: It can heal by fibrosis leaving a residual apical scar.
- Calcification (dystrophic).
- Pleural fibrosis & adhesions.
- Local spread e.g. implantation of bacteria in the larynx leading to hoarseness or bronchial spread leads to bronchopneumonia.
- Systemic spread/miliary TB, via:
  - Vein – via left ventricle to whole body.
  - Artery – miliary spread within the lung.

Miliary Tuberculosis:

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, **Systemic miliary tuberculosis.**

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.



EXTRAPULMONARY TUBERCULOSIS:

TB can affect other organs like:

- **Lymph nodes (tuberculous lymphadenitis):** are the most frequent form of extrapulmonary tuberculosis esp. in the cervical region.
- **Liver and spleen**
- **Adrenals**
- **Fallopian tube and endometrium**
- **Epididymis and prostate**
- **Kidneys**
- **Meninges around the base of the brain (tuberculous meningitis)**
- **Bone marrow**
- **Vertebrae (Pott's disease):** It collapses the spine and leads to paraspinal "cold" abscesses. in these patients, infected material may track along the tissue planes to present as an abdominal or pelvic mass.
- **Intestinal tuberculosis**

PROGNOSIS OF TB:

The prognosis with proper treatment is generally good if infections are localized to the lungs, except 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.

TESTS FOR TUBERCULOSIS

1. Tuberculin (PPD) test: test used to detect the presence of TB

After exposure of TB, and induction of cell mediated immunity, a delayed type hypersensitivity(type 4 hypersensitivity) reaction will occur. In this reaction an influx of macrophages will arrive at the site and cause the "bubble" formation. Intradermal injection with antigenic proteins PPD (Purified Protein Derivative) results in the localized induration and erythema.

People who test positive:

- People who have been exposed to TB
- Vaccinated individuals also can present with a positive test

People who test negative:

- Patient who is not previously exposed to TB
- Severely immunocompromised patients can also present negative (they cant issue cell mediated response)

2. Acid fast bacilli/Ziehl Nielsen stain & Auramine Stain

We don't use Gram stain because Mycoplasma tuberculosis contains high concentrations of mycolic acid in their cell wall which resists the stain.

As a result we either use the Ziehl Nielsen stain or Auramine method.

In the auramine method, we stain the antibody with immunofluorescence stain and then leave it to react with the bacterial antigen. If there is a reaction between them the test is positive

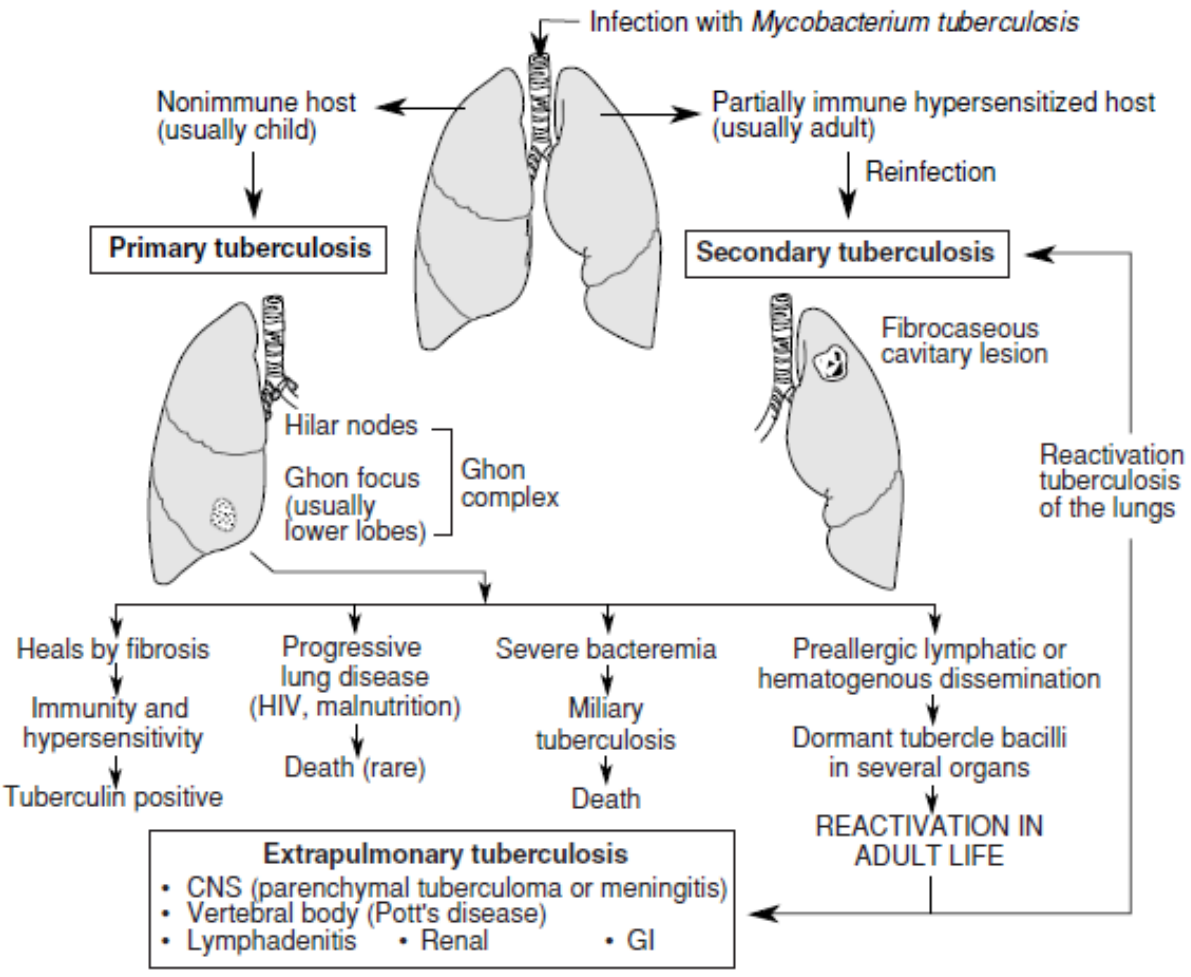
3. Culture in special medium

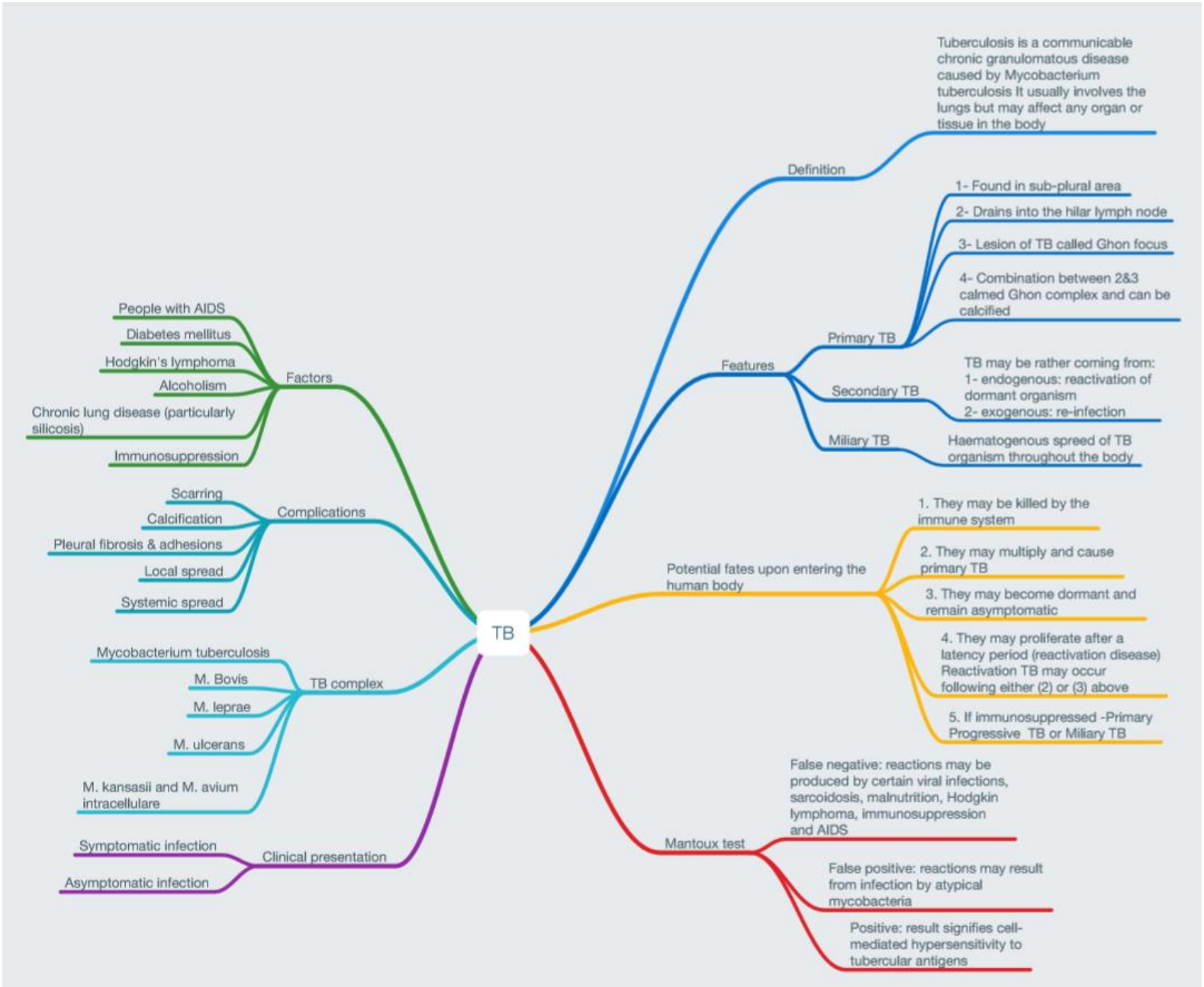
Take a sample and culture is LJ(Lowenstein-Jensen) medium, the culture will take about 2-12 weeks

4. Molecular analysis

PCR (Polymerase chain reaction) a technique used to amplify the DNA of the bacteria to detectable levels. Very accurate and precise

SUMMARY:


Infection with *Mycobacterium tuberculosis*
Nonimmune host (usually child)
Partially immune hypersensitized host (usually adult)
Reinfection
Primary tuberculosis
Secondary tuberculosis
Fibrocaseous cavitary lesion
Hilar nodes
Ghon focus (usually lower lobes)
Ghon complex
Reactivation tuberculosis of the lungs
Heals by fibrosis
Immunity and hypersensitivity
Tuberculin positive
Progressive lung disease (HIV, malnutrition)
Death (rare)
Severe bacteremia
Miliary tuberculosis
Death
Preallergic lymphatic or hematogenous dissemination
Dormant tubercle bacilli in several organs
REACTIVATION IN ADULT LIFE
Extrapulmonary tuberculosis
• CNS (parenchymal tuberculoma or meningitis)
• Vertebral body (Pott's disease)
• Lymphadenitis • Renal • GI


TB
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
Features
Primary TB
1- Found in sub-plural area
2- Drains into the hilar lymph node
3- Lesion of TB called Ghon focus
4- Combination between 2&3 calmed Ghon complex and can be calcified
Secondary TB
TB may be rather coming from:
1- endogenous: reactivation of dormant organism
2- exogenous: re-infection
Miliary TB
Haematogenous spreed of TB organism throughout the body
Potential fates upon entering the human body
1. They may be killed by the immune system
2. They may multiply and cause primary TB
3. They may become dormant and remain asymptomatic
4. They may proliferate after a latency period (reactivation disease) Reactivation TB may occur following either (2) or (3) above
5. If immunosuppressed -Primary Progressive TB or Miliary TB
Mantoux test
False negative: reactions may be produced by certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression and AIDS
False positive: reactions may result from infection by atypical mycobacteria
Positive: result signifies cell-mediated hypersensitivity to tubercular antigens
Factors
People with AIDS
Diabetes mellitus
Hodgkin's lymphoma
Alcoholism
Chronic lung disease (particularly silicosis)
Immunosuppression
Complications
Scarring
Calcification
Pleural fibrosis & adhesions
Local spread
Systemic spread
TB complex
Mycobacterium tuberculosis
M. Bovis
M. leprae
M. ulcerans
M. kansasii and M. avium intracellulare
Clinical presentation
Symptomatic infection
Asymptomatic infection

MCQS

- **1- In the pathogenesis of TB, the activated macrophage secretes:**
- A- IL-12
- B- TNF
- C- Interferon-gamma
- D- IL-10

- **2- immunocompromised patient came with TB at which level the pathogenesis stop:**
- A- TH1 activated
- B- Macrophages
- C- Granuloma formation
- D- Caseous necrosis formation

- **3- It is a combination of ghon focus and the lymph node:**
- A- Granuloma
- B- caseous Necrosis
- C- Ghon complex
- D- Giant cell

- **4- Usually the Ghon focus lesion area is located in:**
- A- Upper part of the lower lobe
- B- Lower part of the lower lobe
- C- Diaphragm
- D- None of them

- **5- M.bovis is acquired by:**
- A- inhalation
- B- contact
- C- drinking of unpasteurized milk
- C- None of them

- **6- The macrophages can recognize M. Tuberculosis by:**
- 1- RANK receptor
- B- Mannose receptor
- C- TNF receptor
- D- None of them

- **7- After doing the Tuberculin skin test the size of induration is measured after:**
- A- 1-2 weeks
- B- 3-6 hours
- C- 48-72 hours
- D- None of them

- **8- When the M.tuberculosis goes to the vertebrae and collapse the spine which leads to paraspinal cold abscesses, This disease called?**
- A- potts disease
- B- Tuberculous meningitis
- C- Renal TB
- D- TB epididymis

1-B 2-B 3-C 4-A 5-C 6-B 7-C 8-A

SAQ

- 1- The Macrophage cannot get rid of the M. tuberculosis because of?
- Mycolic acid
-
- 2- How is the histological appearance of secondary TB?
- Epithelioid granulomas with central caseation and langhan type
-
- 3- The mycobacteria in secondary TB can occur by 2 ways, mention them:
- 1- Reactivation
- 2- Exogenous re-infection

- 4- List three condonation associated with increased risk of TB:
- 1- people with AIDS
- 2- immunosuppression
- 3- Diabetes mellitus

- 5-can mycobacterium tuberculosis bovis transmit by inhalation ?
- NO , it transmit by drinking unpasteurised milk

- 6- why mycobacterium tuberculosis is very strong and tough organism ??
- because it has (glycolipoprotein) in its outer surface which increase resistant to sun , dry atmosphere ...ETC ,

- 7 -how do the macrophages engulf the M.TB??
- they have a receptor for mannose which found in the outer surface of bacteria

- 8 -when the tuberculin test is positive what does that mean ??
- than mean the TH1 get activated and that does not mean the patient have the disease , its mean he met the bacteria before (ex: vaccine)

Males:

Leader : محمد باحاذق

عبدالجبار اليماني

أحمد الراشد

عبدالله بالعبيد

عبدالله السرحاني

أحمد الحربي

أنس السيف

داود إسماعيل

فهد الفايز

محمد بن معيوف

فهد النحابي

سعد الفوزان

سيف المشاري

تميم الوهيبي

خالد العقيلي

محمد الصويغ

محمد الأصقه

السبيعي نواف

عبدالعزيز المحنا

عبدالله المعيذر

فايز الدرسوني

رشيد البلاع

عبدالإله الأحسين

Females:

Leader : بثينة آل ماجد

-فاطمة بالشرف

-رهف الشمري

-رناد الفرم

-هديل عورتاني

-منيرة المسعد

-الجوهرة الشنيفي

-رزان الزهراني

-روان مشعل

-نوف العتيبي

-ابتسام المطيري

-غرام جليدان

-بلقيس الراجحي

-نورة القاضي

-آلاء الصويغ

-ريم القحطاني

-شوق-

PATHOLOGY
TEAM 437

Kindly contact us if you have any questions/comments and suggestions:

* EMAIL: pathology437@gmail.com
* TWITTER : @pathology437

GOOD LUCK! ☺

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*references;

-Robbins Basic Pathology
- doctor's slides