Pathology of TB

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).
- ✓ In regards to Mycobacterial lung infection: Compare and contrast the following in relation to their gross and histologic lung pathology: 1. Primary tuberculosis (include a definition of the Ghon complex). 2. Secondary or reactivation tuberculosis. 3. 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.

Black: original content.
Red: Important.
Green: AlRikabi's Notes.
Grey: Explanation.
Blue: Only found in boys slides.
Pink: Only found in girls slides.

Pathology Teamwork438

MED438 KING SAUD UNIVERSITY

Introduction to TB

Tuberculosis

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. Typically, the centers of tuberculous granulomas undergo caseous necrosis.

Epidemiology

- The World Health Organization (WHO) considers tuberculosis to be the most common cause of death resulting from a single infectious agent, 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:
  1- Poverty
  2-Crowding
  3- Chronic debilitating illness
  4- Malnutrition
- It is considered to be one of the major endemic diseases in the kingdom, particularly involving:
  1- elderly
  2- AIDS patients
  3- Diabetes mellitus
  4- Hodgkin's lymphoma
  5- silicosis patients
  6- the urban poor (low socioeconomic areas)
  7- Alcoholism.

Etiology

Mycobacterium tuberculosis hominis	• It is very aerophilic (strict aerobe, acid fast). Responsible for most cases of tuberculosis, endemic in KSA; the reservoir of infection typically is found in individuals with active pulmonary disease. • Transmission usually is direct, by inhalation of airborne organisms in aerosols generated by expectoration or by exposure to contaminated secretions of infected individuals.
Mycobacterium Avium	• Atypical bacteria, seen ONLY in immunocompromised. • There's no formation of granulomas.
Mycobacterium bovis	• Acquired through drinking unpasteurized milk (from cows), usually starts in the tonsils or Peyer's patches, can cause gastrointestinal tuberculosis in human. It may go to lymph node

Difference between infection and clinical disease: Infection the patient will have the bacteria but he's ASYMPTOMATIC, but when he develop symptoms, we can say he has the disease (Clinical disease).

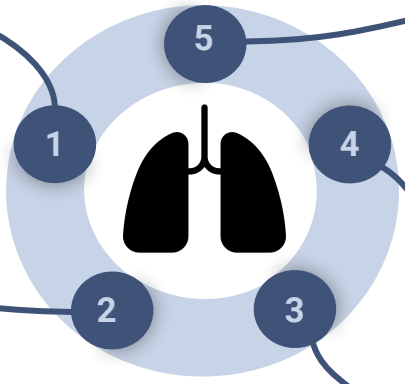
Pathogenesis of TB

Entry into macrophages

A virulent strain of mycobacteria gains entry to macrophage endosomes, a process mediated by several macrophage receptors, including the *macrophage mannose receptor* and *complement receptors* that recognize several components of the mycobacterial cell walls.

Replication in macrophages

Once internalized, the organisms *inhibit normal microbicidal responses* by producing a protein (cord factor) preventing the fusion of the lysosomes with the phagocytic vacuole. allowing the mycobacterium to persist and proliferate. Thus, the earliest phase of primary tuberculosis (the first 3 weeks) in the *non-sensitized* patient is *characterized by bacillary proliferation within the pulmonary alveolar macrophages* and air spaces, eventually *resulting in bacteremia* and *seeding of the organisms to multiple sites*. Despite the bacteremia, most individuals at this stage are asymptomatic or have a mild flu-like illness.



Development of cell-mediated immunity

This occurs approximately 3 weeks after exposure. Processed mycobacterial antigens reach the draining lymph nodes and are presented to CD4 T cells by dendritic cells and macrophages. Under the influence of macrophage-secreted IL-12, CD4+ T cells of the TH1 subset that are capable of secreting IFN-γ are generated.

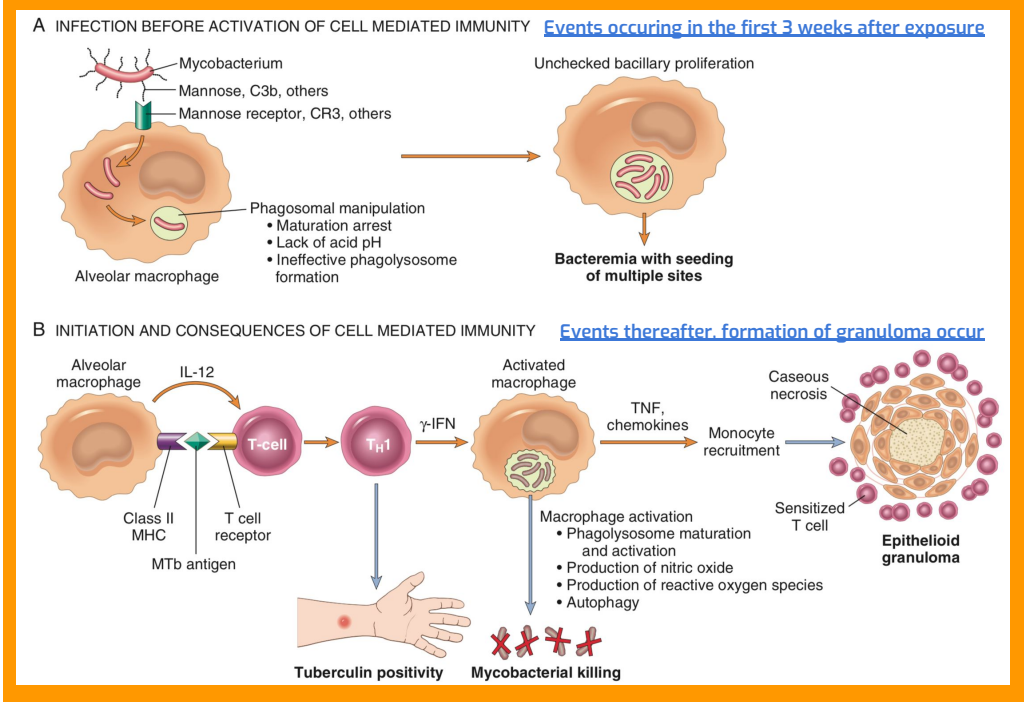
Granulomatous inflammation and tissue damage

- TH1 response orchestrates (organize) the formation of granulomas and caseous necrosis by releasing IFN-γ which cause macrophages to differentiate into epithelioid histiocytes that aggregate to form granulomas. Granuloma is formed three weeks after primary TB exposure.

T cell–mediated macrophage activation and killing of bacteria

IFN-γ released by the CD4+ T cells of the TH1 subset is crucial in activating macrophages. Activated macrophages, in turn, release a variety of mediators + chemokines and upregulate expression of genes with important downstream effects including: TNF (responsible for recruitment of monocytes), Nitric Oxide synthase (iNOS) (raises NO levels) and defensin (anti-microbial peptides which is toxic to M.TB).

A graph illustrating the sequence of events from inhalation of the infectious inoculum to containment of the Primary TB (First time exposure to TB):



Note that:

- Histiocytes are inactive in phagocytosis, while macrophages are active

- Defects in any of the steps of a TH1 T cell response (including IL-12, IFN-γ, TNF, or NO production) result in poorly formed granulomas, absence of resistance, and disease progression.

- Individuals with inherited mutations in any component of the TH1 pathway are extremely susceptible to infections with mycobacteria.

- 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. Just as hypersensitivity and resistance appear in parallel, so, too, the loss of hypersensitivity is an ominous sign of fading resistance to the organism.

Differentiation:

Septicemia	• Proliferation of the organism within the blood causing an infection & activating a systemic immune response (not caused by TB).
Bacteremia	• Presence of the bacteria within the blood, without causing an infection (caused by TB).

Types of TB

Primary TB

(The majority of cases are Asymptomatic)

Definition: Primary tuberculosis is the form of disease that develops in a previously unexposed and therefore unsensitized patient. Happens within the first three weeks of exposure.

Site: Distal air spaces of the lower part of the upper lobe or in the upper part of the lower lobe, typically close to the pleura.

Morphology

Stage I

Ghon focus

1 to 1.5 cm area of gray-white inflammatory consolidation

Emerges during the development of sensitization. Usually, the center of this focus undergoes caseous necrosis.

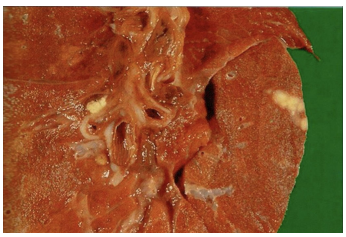
Located peripherally

Stage II

Ghon complex

Ghon focus + Nodal lesions

Tubercle bacilli, either free or within phagocytes, travel via the lymphatic vessels to the regional lymph nodes which also often caseate.



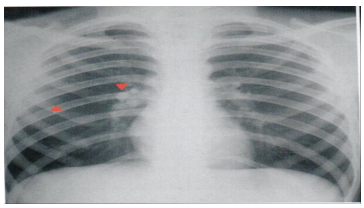
Stage III

Ranke complex

Healed primary pulmonary tuberculosis

"Detectable on radiograph"

Development of cell-mediated immunity controls the infection in approximately 95% of cases, therefore the ghon complex undergoes progressive fibrosis, followed by calcification.



Ghon's complex:

- Location: subpleural area. Upper parts of the lower lobes or lower parts of upper lobes (mid lung)

Uncommonly, new infection leads to progressive primary tuberculosis:

The incidence of progressive primary tuberculosis is particularly high in HIV-positive patients with significant immunosuppression (i.e., CD4+ T-cell counts below 200 cells/μl).

Why?

Immunosuppression results in an inability to mount a CD4+ T cell–mediated response that would contain the primary focus.*

*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 secondary TB.

Types of TB

Secondary TB

Definition: **Secondary tuberculosis is the pattern of disease that arises in a previously sensitized host, it arises due to reactivation of dormant primary lesions or due to reinfection.**

It forms Cavitary foci of caseous necrosis: The risk of spread of infection to non-infected persons from individuals with cavitary tuberculosis is very high. Why? **because the patient now coughs sputum that contains bacilli, therefore patient should be isolated for 10-14 days from starting treatment.**

Site: **Classically localized to the apex of one or both upper lobes.**
Why? **The reason is obscure but may relate to high oxygen tension in the apices**"remember M.TB is a strict aerobe.".

NOTE: The regional lymph nodes are less prominently involved early in the disease than they are in primary TB.

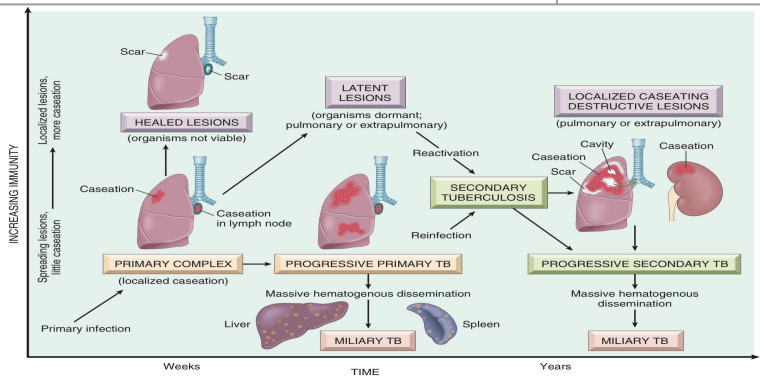
It may complicate to:

Miliary Tuberculosis

MTB can rupture the macrophages and escape into the bloodstream via lymphatic vessels,

- The word miliary is derived from the resemblance of these foci to millet seeds.
- It can go anywhere & symptoms depend on the location.
  E.g. Liver, bone marrow, meninges fallopian tubes and epididymis.

Systemic miliary TB	Isolated-organ TB (Extrapulmonary TB)	Pulmonary miliary TB
• Ensues when the organisms disseminate hematogenously throughout the body. • Systemic miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenal glands, meninges, kidneys, fallopian tubes, and epididymis. • Multiple small yellow nodular lesions in several organs (Almost every organ in the body may be seeded. Lesions resemble those in the lungs).	• **May appear in any one of the organs or tissues seeded hematogenously.** • **Organs typically involved include:** - **Lymph nodes (tuberculous lymphadenitis):** are the most frequent form of extrapulmonary tuberculosis esp. in the cervical region **"Scrofula".** - **Pleura with pleural effusion (exudate)** - **Liver, spleen, kidneys and Adrenals glands.** - **Fallopian tube (Tuberculous salpingitis) and endometrium** - **Epididymis and prostate** - **meninges (tuberculous meningitis),** - **Bone marrow and Vertebrae (Pott's disease)** - **Intestinal tuberculosis.**	• Occurs when organisms reach the bloodstream through lymphatic vessels and then recirculate to the lung via the pulmonary arteries. • The lesions appear as small (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma.



Clinical features of TB

Clinical presentation:

- Localized secondary tuberculosis may be asymptomatic.
- Manifestations are usually insidious in onset.
- Systemic manifestations, probably related to the release of cytokines by activated macrophages (e.g., TNF and IL-1).

Malaise	Anorexia (malnutrition)
Weight loss	Fever "Commonly, the fever is low grade and remittent"
Night sweats	With progressive pulmonary involvement, increasing amounts of sputum, at first mucoid and later purulent appear..
Pleuritic pain "Due to extension of infection to the pleural surfaces"	Cough or/and hemoptysis

What if the mycobacterium spread, will the manifestations change?

Yes, extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved, For example:

1- Tuberculous salpingitis may present as infertility.
2- Tuberculous meningitis may present as headache and neurologic deficits.
3- Pott disease may present with back pain and paraplegia

Ways in which we can obtain a specimen

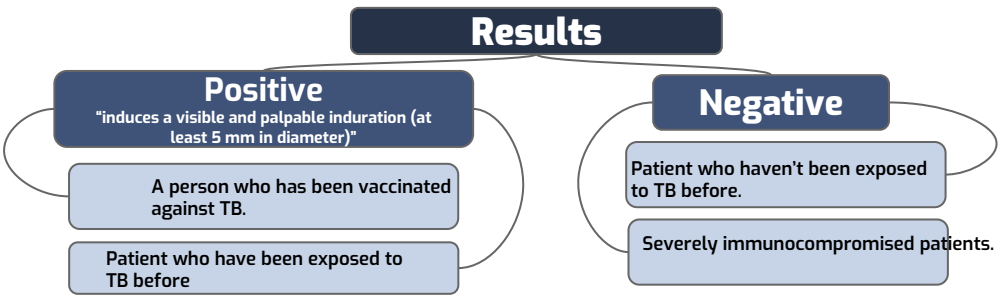
- Bronchoalveolar lavage*
- 3 Early morning sputum or urine
- lymph nodes, Pus or tissue not swab
- CSF
- Joint, bone aspiration

* is a medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid squirted into a small part of the lung and then collect for examination.

Tests for TB

PPD
Purified Protein Derivative
(also called tuberculin test or heaf test)

- A cell-mediated immunity will occur and that will result in a localized delayed hypersensitivity reaction type 4.
  "resulting from macrophage reaction and interaction with CD4 T cells which got transformed to TH2 cells Through IL-12 at 3rd week."
- So we can you use this reaction to our advantage to test for TB by using 0.1ml PPD Intradermal injection of antigenic protein particles from killed M.TB If the test is positive will result in localized skin induration (5+mm) and erythema 3 days after injection.
- The size of induration is measured 48– 72 hours later
- 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
- **Does NOT differentiate between infection and disease.**



Lowenstein - Jensen
(culture)

- We can test the susceptibility to different antibiotics
- LJ is a medium that we can culture M.TB on.
- It takes 2-12 weeks. (10 weeks)
- liquid media can give results in 2 weeks

AFB
(Acid Fast Bacilli) or (carbol fuchsin)
Ziehl-Neelsen

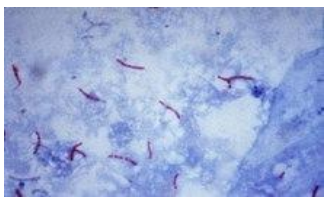
- We don't use gram stain because M.TB contain high lipid concentration (Mycolic acid) in their cell wall, which resists staining. It has an atypical cell wall.
- Therefore After taking a smear we'll use either Ziehl Neelsen method or the auramine stain.

Auramine stain

- **A stain that involves staining the antibody with an immunofluorescence dye and then reacting it with the antigen of the bacteria.**
- **If there is a reaction then it is positive.**

PCR
(Polymerase chain reaction)

- It is a method that recognize the DNA of the bacteria via molecular means.
  this is very accurate. it might give false positive because it's sensitivity. there are no limiting factors such as a time, amount of specimen, or even deterioration of the tissue. It takes around two days or so to obtain the results.



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).

Granuloma

Granuloma

Definition

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.

Tuberculosis is a granulomatous disease.

Caseation

Fibrous connective tissue often surrounds granulomas (remodelling of tissue).

In TB areas within the granuloma can undergo necrosis (caseous necrosis).

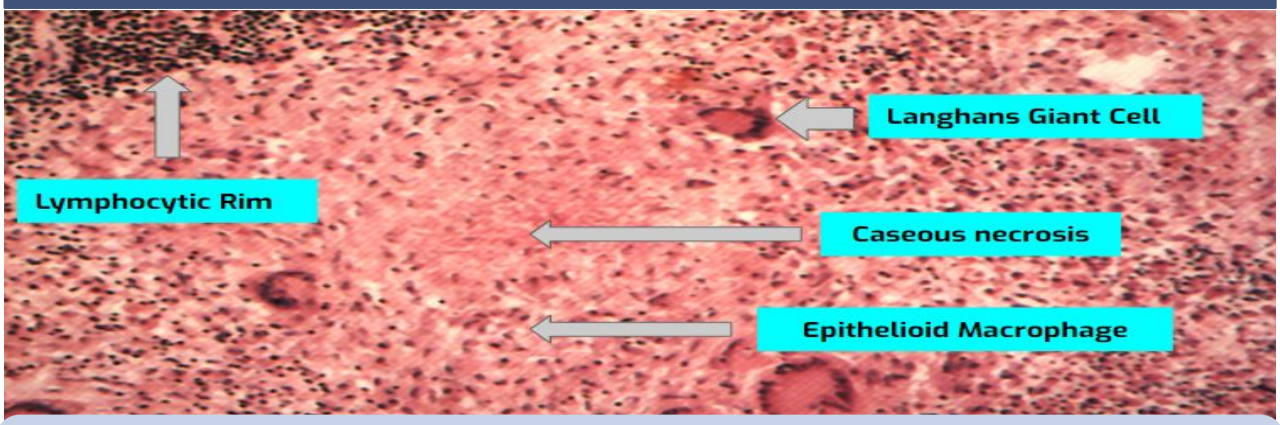
Necrosis can lead to calcification. TB granulomas are called tubercles, and if they are caseating in the center, they are called soft tubercles.

Giant cells

Epithelioid cells fuse to form giant cells containing 20 or more nuclei. The giant cells can be found either at periphery or at the center of the granuloma.

The nuclei are arranged either peripherally (langhans-type giant cells) or haphazardly (foreign body-type giant cells). Both Langhans ("Classic TB") and foreign-body giant cells are common.

Morphology of Granulomas in TB (Tubercles):



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.

After biopsy and seeing granulomas, recall that sarcoidosis and crohn's disease both form granuloma. So, ask for where the patient is from to determine if it's TB.

Summary

Tuberculosis

General considerations	• Tuberculosis occurs worldwide, with greatest frequency in disadvantaged groups. • In the pulmonary form, it is spread by inhalation of droplets containing the organism Mycobacterium tuberculosis (also referred to as the tubercle bacillus).
Types of tuberculosis	• **Primary TB:** - It's the initial infection, characterized by the Ghon complex, the combination of a peripheral subpleural parenchymal lesion and involved hilar lymph nodes. - Primary tuberculosis is most often asymptomatic. It usually does not progress to clinically evident disease. • **Secondary TB:** - Usually results from activation of a prior Ghon complex, with spread to a new pulmonary or extrapulmonary site.
Pathologic changes	**A.** Localized lesions: usually in the apical or posterior segments of the upper lobes. Involvement of hilar lymph nodes is also common. **B.** Tubercle formation: The lesions frequently coalesce and rupture into the bronchi. The caseous contents may liquefy and be expelled, resulting in cavitary lesions. Cavitation is a characteristic of secondary, but not primary, tuberculosis; caseation (a manifestation of partial immunity) is seen in both. **C.** Scarring and calcification.
Spread of disease	**A.** Secondary tuberculosis may be complicated by lymphatic and hematogenous spread, resulting in miliary tuberculosis, which is seeding of distal organs with innumerable small millet seed-like lesions. **B.** Hematogenous spread may also result in larger lesions, which may involve almost any organ. **C.** Organs typically involved include: Meninges, fallopian tube" Tuberculous salpingitis", vertebrae"Pott disease", Lymphadenitis in the cervical region "Scrofula".

Dr. AlRikabi's notes

Tuberculosis

Definition: Chronic bacterial inflammatory condition (more common in low socioeconomic areas), Increased recently due to AIDS epidemic (immunocompromised patients).

Etiology:
- M. Hominis (human—>transmitted via aerial droplets)
- M. Bovis (cows—>transmitted through unpasteurized milk—>goes to lymph node)
- M. Avium (atypical—>only in immunocompromised—>No granulomas)

Common symptoms of pulmonary TB:
Drenching night sweats, Malnutrition, Cough, Weight loss, Fever, Hemoptysis.

Pathogenesis:
1- MTB will adhere to alveolar macrophages (first cell infected).
2- It will resist phagocytosis and proliferate inside (earliest phase of primary TB, 1st 3 weeks).
3- Macrophages present MTB antigen to CD4+ cells and will secrete IL-12.
4- IL-12 allows CD4+ cells to become Th1 (Type IV hypersensitivity reaction), secreting IFN-γ.
5- IFN-γ activates macrophages into releasing TNF, iNOS, and defensins.
- TNF—>recruitment of monocytes, which become epithelioid histiocytes, some of which fuse into giant cells.
- iNOS—>Increase levels of NO.
- defensins—>toxic to MTB.
6- IFN-γ also causes granulomas and caseous necrosis
- Macrophages activated by IFN-γ differentiate into epithelioid histiocytes that aggregate to form granulomas.
- Those macrophages also secrete TNF and chemokines, which recruit even more monocytes.
- In immunocompromised patients, the ongoing immune response results in caseous necrosis.

Secondary

Definition: Reactivation of primary TB or reinfection.

Miliary TB:
- MTB can rupture the macrophages and escape into the bloodstream via lymphatic vessels, and it can either be:

1- **Pulmonary miliary TB.**
2- Spread to other organs:
Multiple organs—>**systemic miliary TB**.
Single organ—>**Isolated-organ TB**.

Lymphadenitis:
- Most frequent form of extrapulmonary tuberculosis, occurs in the cervical region.
- Scrofula (enlarged lymph nodes with caseous granuloma),
- Commonly caused by M. Bovis.

In case of disease progression:
- Granulomas erode the bronchi or trachea —>spread caseous material via cough—>open/cavitating tuberculosis.

Primary

Definition: Initial infection

Ghon Focus:
- Always peripheral (sub-pleural—>upper part of lower lobe or lower part of upper lobe).

Ghon complex:
- Ipsilateral (same side) enlarged hilar lymph node..

Treatment: "It's explained better in pharmacology"
Triple therapy for a long period of time, 6 months -2 years

Quiz

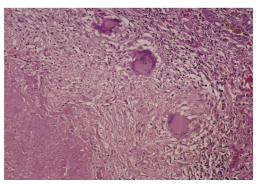
1) A 22-year-old man with AIDS complains of persistent cough, night sweats, low-grade fever, and general malaise. A chest X-ray reveals an area of consolidation in the periphery of the left upper lobe, as well as hilar lymphadenopathy. Sputum cultures show acid-fast bacilli. Which of the following is the most likely diagnosis?

(A) Bronchopneumonia
(B) Pulmonary abscess
(C) Sarcoidosis
(D) Tuberculosis
(E) Wegener granulomatosis

2) A 53-year-old man develops weakness, malaise, cough with bloody sputum, and night sweats. A chest X-ray reveals numerous apical densities bilaterally, some of which are cavitary. Exposure to Mycobacterium tuberculosis was documented 20 years ago, and M. tuberculosis is identified in his sputum. Which of the following describes the expected lung pathology in this patient?

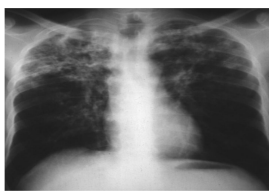
(A) Dense fibrosis
(B) Eosinophilic infiltration
(C) Granulomas
(D) Interstitial pneumonia
(E) Plasma cell infiltration

3) A 46-year-old woman has a routine health maintenance examination. On physical examination, there are no remarkable findings. Her body mass index is 22. She does not smoke. A tuberculin skin test is positive. A chest radiograph shows a solitary, 3-cm left upper lobe mass without calcifications. The mass is removed at thoracotomy by wedge resection. The microscopic appearance of this lesion is shown in the figure. Which of the following is the most likely diagnosis?



(A) Necrotizing granulomatous vasculitis
(B) Poorly differentiated adenocarcinoma
(C) Thromboembolism with infarction
(D) Staphylococcus aureus abscess
(E) Mycobacterium tuberculosis infection

4) A 56-year-old man has had fever, night sweats, and a 3-kg weight loss over the past 4 months. In the past month, he has had episodes of hemoptysis. On physical examination there are upper lobe rales. He has hypoxemia. The appearance of his chest radiograph is shown in the figure. He is most likely to have an infection with which of the following organisms?



(A) Candida albicans
(B) Influenza A
(C) Legionella pneumophila
(D) Mycobacterium tuberculosis
(E) Mycoplasma pneumoniae

5) The chest radiograph of a 23-year-old medical student reveals a calcified cavitary pulmonary lesion. The tuberculin test is positive, but sputum smears and cultures are negative for Mycobacterium tuberculosis. A presumptive diagnosis of secondary tuberculosis is made. If further studies, including a biopsy, were performed, which of the following findings would justify the diagnosis of secondary tuberculosis, as contrasted to primary tuberculosis?

(A) Positive tuberculin test result
(B) Langhans giant cells
(C) Caseating granulomas
(D) Calcification
(E) Cavitation

Answer Explanation File

1- D | 2- C | 3- E | 4- D | 5- E

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Thank you

Pathology
Teamwork438