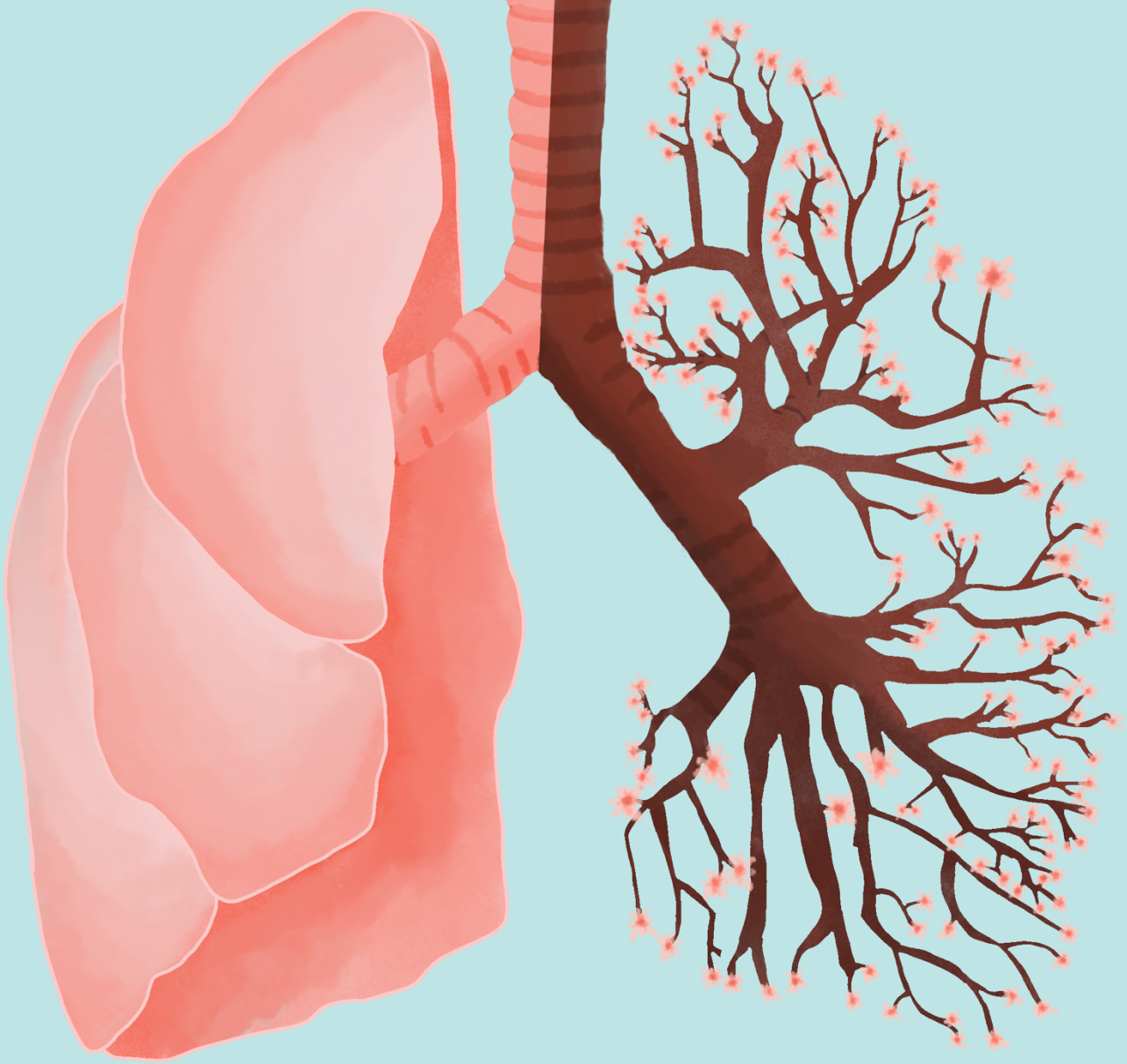
RESPIRATORY SYSTEM PATHOLOGY



Title: Sheet 9 – Tuberculosis

Writer: Alia Abbadi

Science: Mohmmad Yousef

Final: Nasser M. Abdelqader

Doctor: Maram Abdaljaleel

In this lecture, we'll be covering some aspects regarding tuberculosis; including epidemiology, risk factors, etiology, pathogenesis, diagnosis and prognosis. Enjoy.

TUBERCULOSIS

Tuberculosis is a communicable chronic granulomatous disease caused by Mycobacterium tuberculosis. It usually involves the lungs but may affect any organ in the body.

Epidemiology

- Tuberculosis (TB) is considered by the World Health Organization to be the most common cause of death resulting from a single infectious agent.
- Tuberculosis flourishes under conditions of poverty, crowding, and chronic debilitating illness. The following groups are at highest risk to develop TB in the U.S:

older adults	*The Inuit (from Alaska)*	*Chronic renal failure*
The urban poor	*Hispanics*	*Malnutrition*
Patients with AIDS	*Immigrants from Southeast Asia*	*Alcoholism*
Members of minority communities	*Diabetes mellitus*	*Immunosuppression*
African Americans	*Hodgkin lymphoma*	*HIV*
Native Americans		*Chronic lung disease (particularly silicosis)*

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

Infection VS disease

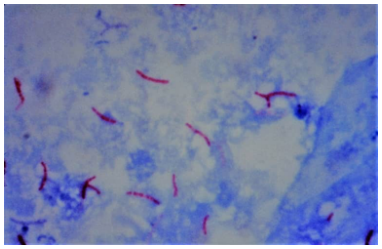
It is important to know the difference between an infection and a disease. An Infection refers to seeding of a focus in the body with organisms, which *may or may not* cause **clinically significant** tissue damage.

What if clinically significant tissue damage does occur? Now, that's called a disease.

Route of transmission

Most infections are acquired by direct person-to person transmission of airborne droplets of organisms from an **active case** to a susceptible host.

Etiology



Mycobacteria are slender bacilli (rods) that are acid-fast (i.e., they have a high content of complex lipids that bind the Ziehl-Neelsen and resist decolorization). *ZN stained specimen is shown on the right, TB bacilli are pink/purple colored.*

- Mycobacterium tuberculosis hominis is responsible for most cases of tuberculosis; 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 bovis causes oropharyngeal and intestinal tuberculosis. It is usually contracted by drinking milk contaminated with the bacterium. However, infections by M. bovis are now rare except in countries with tuberculous dairy cows and sales of unpasteurized milk.
- Mycobacterium avium complex are much less virulent than M. tuberculosis and rarely cause disease in immunocompetent individuals. However, they are responsible of TB in 10% to 30% of patients with AIDS.

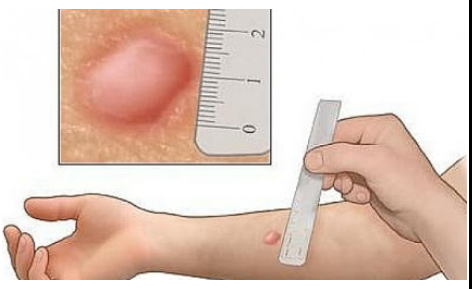
Primary tuberculosis

- It is the initial infection that develops in a previously **unexposed** and **unsensitized** patient.
- Usually in children.
- In nearly all cases, granulomas that develop during this phase, resolve and there is no further spread of infection

- Scenarios that might occur following primary TB infection:
  - In most individuals, the only consequence of primary tuberculosis are the **self-limited asymptomatic** foci of scarring due to pulmonary infection, i.e. the only evidence of infection, if any remains, is a tiny, telltale **fibrocalcific** nodule at the site of the infection. Viable organisms may remain dormant in such foci for decades, and possibly for the life of the host. Such individuals are **infected but *do not* have active disease** and therefore cannot transmit organisms to others.
    - ⇨ Yet, if their immune defenses are lowered, the infection may **reactivate** to produce communicable and potentially life-threatening disease (*secondary TB, we'll talk about it soon*)

  - Uncommonly (5% ONLY of those newly infected), may acquire significant disease characterized by fever and pleural effusions.

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



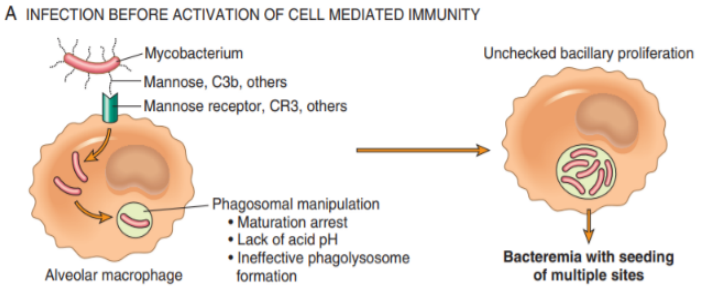
  - Intracutaneous injection of 0.1 mL of sterile purified protein derivative (PPD)
    - ⇨ Positive test: if it induces a visible and palpable induration (at least 5 mm in diameter) that usually peaks in 48 to 72 hours.
    - ⇨ Negative test: means that you most likely haven't been infected with the bacteria.
  - Test limitations:
    - ✓ A positive test does not differentiate between infection and disease.
    - ✓ False-negative reactions may be related by certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression, and the presence of an overwhelming active tuberculous disease.
    - ✓ False-positive reactions may result from infection by atypical mycobacteria.

▪ Pathogenesis of primary TB

The pathogenesis of tuberculosis in the previously unexposed immunocompetent individual is centered on the development of **cell-mediated immunity.** Cell-mediated immunity provides **resistance** to the organism and results in development of **tissue hypersensitivity** to tubercular antigens. The characteristic pathologic features of TB, such as caseating granulomas and cavitation, are the result of the destructive tissue hypersensitivity that is part of the host immune response.

The sequence of events involved in the pathogenesis (*I.e. the events involved in the natural history of primary pulmonary TB*), is going to be divided into two stages;

1) **Infection before activation of cell immunity**. (*during the first 3 weeks after exposure*). Here's what happens during this period:



A- Inhalation of virulent strains of Mycobacterium.

B- Entry into macrophages

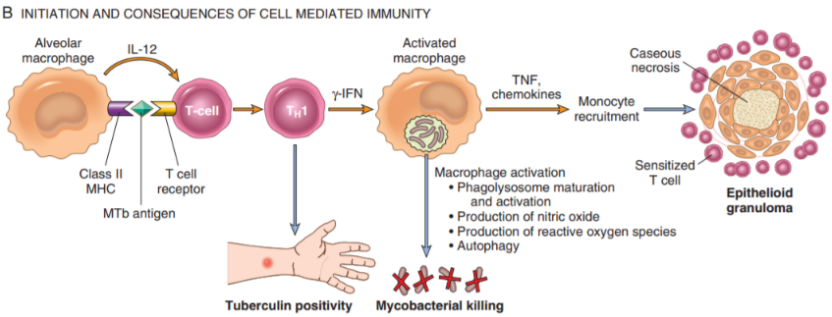
A virulent strain of mycobacteria gains entry to macrophage endosomes, a process mediated by several macrophage receptors, including the macrophage mannose receptor and complement receptors that recognize several components of the mycobacterial cell walls.

C- Replication in macrophages.

Once internalized, the organisms **inhibit the macrophage's microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole** → This allows the mycobacterium to persist and proliferate.

Thus, the earliest phase of primary TB (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 flulike illness.

2) **Development of cell mediated immunity** (*the following events take place approximately 3 weeks after exposure)*. 7:57



A- Under the influence of *macrophage-secreted **IL-12***, T helper 1 that are capable of secreting IFN-γ are generated.

B- IFN-γ released by type 1 T helper cells is crucial in activating macrophages → Activated macrophages release a variety of mediators and upregulate expression of genes with important downstream effects, including:

I. **TNF**, which is responsible for recruitment of monocytes.
II. **Inducible nitric oxide synthase (iNOS)**, which raises nitric oxide (NO) levels, helping to create reactive nitrogen intermediates that are important in killing of mycobacteria.
III. **Anti-microbial peptides (defensins)** which are also toxic to the bacteria.

C- Granulomatous inflammation and tissue damage.

- Type 1 T helper lymphocytes (TH1) aid in the formation of granulomas and caseous necrosis.
- Macrophages activated by IFN-γ, differentiate into the "epithelioid histiocytes" that aggregate to form granulomas; some epithelioid cells may fuse to form giant cells.
  - ⇨ This response, in many individuals, halts the infection before significant tissue destruction or illness occur.
  - ⇨ In other individuals with immune deficits due to age or immunosuppression, the infection progresses and the ongoing immune response results in caseation necrosis. Furthermore, activated macrophages also secrete TNF and chemokines, which promote recruitment of more monocytes.

Notes about the immune response to TB

- As mentioned above, Immunity to a TB 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.
- A positive result on tuberculin skin testing (Mantoux) is a result of the development of immunity and resistance to the organism.

- What ifs:

1- What if there is reactivation of the infection or re-exposure to the bacilli in a previously sensitized (*and still immunocompetent*) host?

Rapid mobilization of a defensive reaction occurs accompanied by increased tissue necrosis.

2- What if there is loss of hypersensitivity?

Just as hypersensitivity and resistance to the bacteria appear in parallel, so, too, the loss of hypersensitivity (*indicated by negative Mantoux test in a M. tuberculosis-infected patient*) is an ominous (bad) sign of **fading resistance** to the organism.

3- What if there is a defect in the immune response?

Defects in any of the steps of a type 1 helper T cell response → result in poorly formed granulomas, absence of resistance, and disease progression.

Primary Tuberculosis, presentation:

In the large majority of otherwise healthy individuals, the only consequence of primary tuberculosis are foci of scarring which may harbor viable bacilli and serve as a nidus for disease reactivation at a later time if host defenses wane.

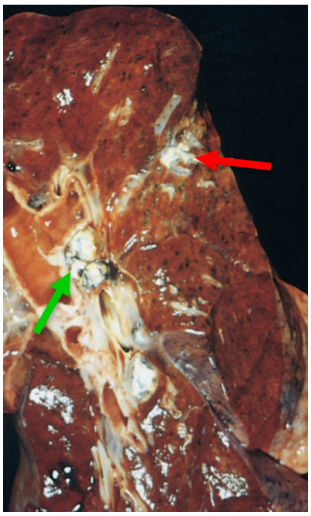
Morphology of primary tuberculosis 13:00

- ✓ In countries in which bovine TB and infected milk have largely disappeared, primary tuberculosis almost always begins in the lungs.
- ✓ The inhaled bacilli usually implant in the distal air spaces of the **lower part of the upper lobe or in the upper part of the lower lobe** and are typically close to the pleura.

- ✓ During the development of sensitization, a 1-1.5 cm area of gray-white inflammatory consolidation* emerges. This is called the Ghon focus. In most cases, the center of this focus undergoes caseous necrosis. Tubercle bacilli, either free or within phagocytes, travel via the lymphatic vessels to the regional lymph nodes, which also often caseate. This combination of parenchymal and nodal lesions is called the Ghon complex *(can be seen grossly as in the picture)*

  Red arrow → gray-white parenchymal focus located under the pleura in the lower part of the upper lobe. (Ghon focus)

  Green arrow → Hilar lymph nodes with caseation. Together they are called Ghon complex.



*Consolidation describes the presence of exudate in the airways and alveoli, usually as a result of infection. Remember pleural effusion? Consolidation is like it, but it occurs in the **lung's parenchyma** not the pleura.

- ✓ Cell-mediated immunity, which controls the infection in approximately 95% of cases, results the following:
  - Progressive fibrosis, and calcification of the Ghon complex. (fibrocalcific nodule)
  - NO lesions in other organs occur, despite lymphatic and hematogenous dissemination and seeding of different organs during the first few weeks.

- ✓ Histologically, sites of infection are involved by a characteristic inflammatory reaction marked by the presence of caseating and non-caseating granulomas, which consist of epithelioid histiocytes and multinucleate giant cells. The figures show the morphologic spectrum of TB.

Figure (A) → characteristic tubercle at low magnification

Figure (B) → Same tubercle at higher magnification
The tubercle shows central granular caseation *(blue arrow)* surrounded by epithelioid and multinucleate giant cells *(orange arrow).* This is the usual response in individuals who develop cell-mediated immunity to the organism.

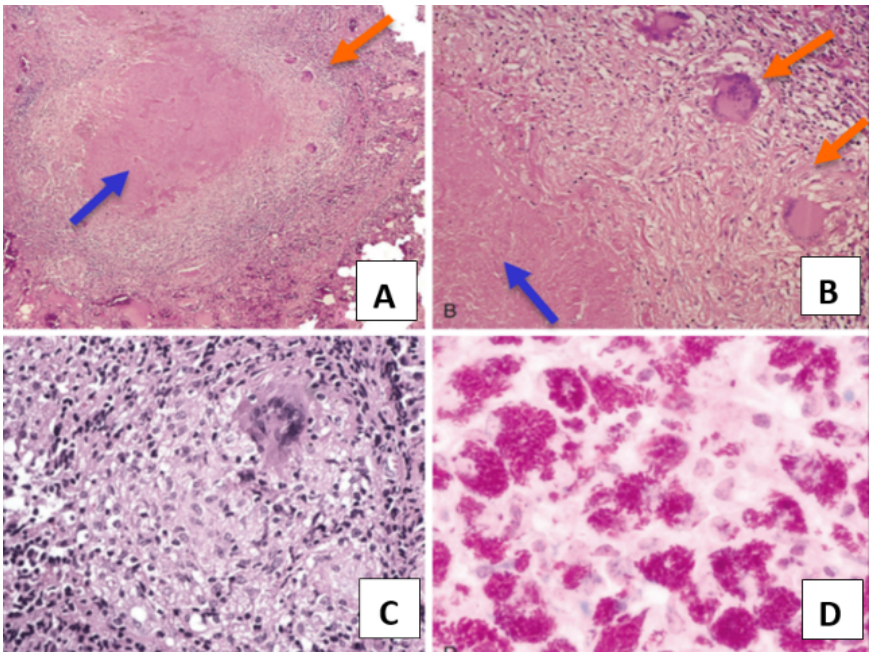


Figure (C) → Occasionally, even in immunocompetent patients, tubercular granulomas may not show central caseation. Regardless if caseous necrosis is present or absent, use of *special* stains for acid-fast organisms is indicated when granulomas are present.

Figure (D) → In this specimen from an immunosuppressed patient, sheets of macrophages packed with mycobacteria are seen (acid-fast stain)

Secondary Tuberculosis (Reactivation Tuberculosis)

- It is the pattern of disease that arises in a **previously sensitized** host by reactivation of previous infection. It appears many decades, particularly when host health status. It may also result from reinfection.
- Only a few patients with primary disease subsequently develop secondary TB.
- Occurs mostly in adults.
- Secondary pulmonary TB is classically localized to **the apex of one or both upper lobes.**
- Because of the preexistence of hypersensitivity, marked tissue response that tends to wall off *(separate)* the focus takes place. As a result of this localization, the regional lymph nodes are less prominently involved if compared with primary TB. On the other hand, cavitation occurs readily in the secondary form, leading to erosion into and dissemination along airways. Such changes become an important source of infectivity, because the patient **now produces sputum containing bacilli**.
    - ⇨ So, lymph node involvement is more common in primary TB while cavitation is more common in secondary TB.

Morphology of secondary TB

- The initial lesion usually is a small focus of consolidation, less than 2 cm in diameter, within 1-2 cm of the **apical** pleura. Such foci are sharply circumscribed, firm, gray-white to yellow areas that have a variable amount of central caseation and peripheral fibrosis. *(Grossly)*
- Histologically, the active lesions show characteristic coalescent tubercles with central caseation.
- Although tubercle bacilli can be demonstrated in early exudative and caseous phases of granuloma formation, it is usually impossible to find them in the late, fibrocalcific stages.

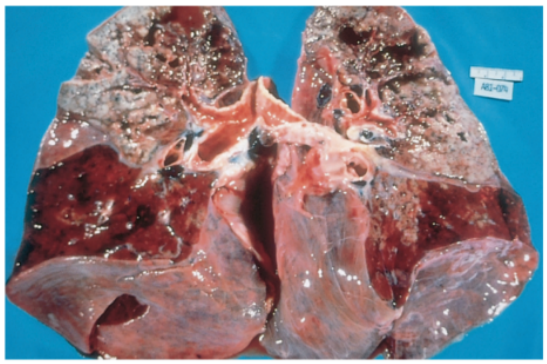


Fig. 13.36 Secondary pulmonary tuberculosis. The upper parts of both lungs are riddled with gray-white areas of caseation and multiple areas of softening and cavitation.

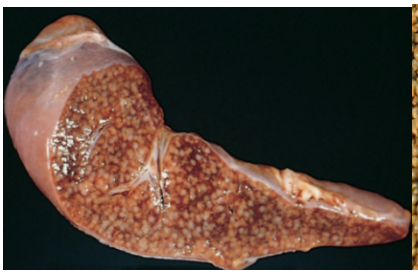
- Secondary tuberculosis may heal with fibrosis either spontaneously or after therapy. Otherwise, the disease may progress and extend along several different pathways:

Progressive pulmonary tuberculosis:

A. Uncommon
B. The **apical** lesion enlarges, and the area of caseation expands.
C. Erosion into a bronchus evacuates the caseous center, creating a ragged, irregular cavity lined by caseous material that is poorly walled off by fibrous tissue.
D. Erosion of blood vessels results in hemoptysis.
E. With **adequate treatment** the process may be arrested. However, the fibrosis that occurs often resulting in distortion of the pulmonary architecture.
F. If the treatment is inadequate or host defenses are impaired, the infection may spread by direct extension and by dissemination through airways, lymphatic channels, and the vascular system.

✓ Now, if organisms reach the bloodstream through lymphatic vessels and then recirculate to the lung via the pulmonary arteries, small lesions of yellow-white consolidation scattered through the lung parenchyma appear, resulting in what's called **miliary pulmonary disease**. *(The word miliary is derived from the resemblance of these foci to millet seeds).*

✓ **Systemic miliary tuberculosis** ensues when the organisms disseminate hematogenously throughout the body. Most prominently in the liver, bone marrow, spleen, adrenal glands, meninges, kidneys, fallopian tubes, and epididymis. Look at the pictures of millet seeds and miliary TB of the spleen showing grey-white granulomas, notice the resemblance between them.



✓ **Isolated-organ TB** may appear in any one of the organs or tissues seeded hematogenously. Organs typically involved include the meninges, kidneys, adrenal glands, bones and fallopian tubes. When the vertebrae are affected, the condition is referred to as **Pott disease.**

Clinical Features they are related to the different outcomes previously discussed. 20:50

- ♣ The disease be clinically asymptomatic in **localized** secondary TB.
- ♣ Systemic manifestations, *related to the release of cytokines by activated macrophages (e.g., TNF and IL-1)*, often appear **early** in the disease course and include malaise, anorexia, weight loss, and fever.
  - ⇨ Commonly, the fever is low grade appearing late each afternoon and then subsiding +/- night sweats.
- ♣ When cavitation is present, the sputum contains tubercle bacilli.
- ♣ Some degree of hemoptysis is present in about half of all cases of pulmonary TB.
- ♣ Pleuritic pain may result from extension of the infection to the pleural surfaces.
- ♣ Extrapulmonary manifestations of TB depend on the organ system involved.

Diagnosis

The diagnosis of pulmonary disease is based on the history, physical and radiographic findings of consolidation or cavitation in the apices of the lungs. Ultimately, however, tubercle bacilli must be identified using the following methods:

The most common method: Demonstration of acid-fast organisms in sputum by staining or by use of fluorescent auramine rhodamine.	The standard diagnostic method: Conventional cultures, which may require up to 10 weeks but remain the standard method because ***they can identify the occasional PCR-negative case and allow testing of drug susceptibility***.
PCR amplification.	Liquid media–based radiometric assays that can provide an answer within 2 weeks.

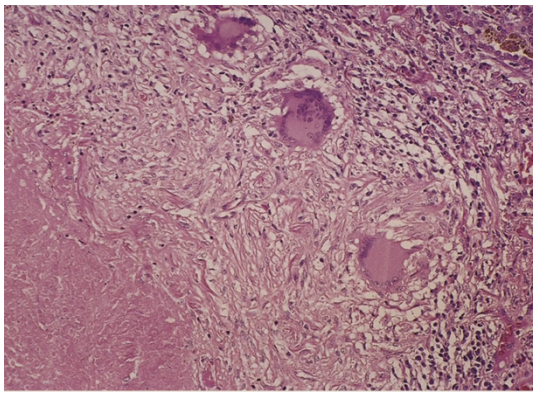
Prognosis

It is determined by:

- The extent of the infection (localized versus widespread)
- The immune status of the host.
- The antibiotic sensitivity of the organism.

Clinical cases

1) 45-year-old lady 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 (TST)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?

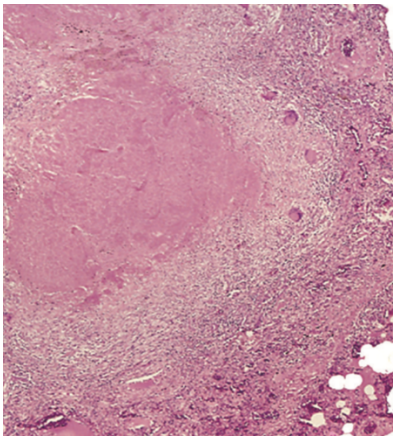


A Mycobacterium tuberculosis infection
B Necrotizing granulomatous vasculitis
C Poorly differentiated adenocarcinoma
D Staphylococcus aureus abscess
E Thromboembolism with infarction

Answer: A.

Explanation:
Due to the positive TST test, the radiographic findings and the histologic picture showing pink amorphous tissue on the lower left corner and epithelioid cells.
Note: if it was mentioned that there IS some calcification, it would've been easier to identify the mass as an old granuloma not a neoplasm.

2) A 39-year-old gentleman had cough with a low-grade fever and a 4-kg weight loss over the course of 3 months. A lung biopsy is performed as in the figure. An acid-fast stain of this tissue is positive. The causative infectious agent is most likely being destroyed by which of the following mechanisms?



A Complement-mediated lysis
B Elaboration of nitric oxide by macrophages
C Phagocytosis by eosinophils
D Superoxide formation within phagolysosomes

Answer: B

Explanation:
• The figure shows a caseating granuloma.
• Activated macrophages are the key cellular component within granulomas that form to control persistent organisms such as M. tuberculosis. As part of delayed type hypersensitivity with a TH1 immune response, CD4+ cells secrete interferon-γ, which activates macrophages to kill organisms with reactive nitrogen intermediates.

• Why not A? Complement-mediated lysis is not involved in the destruction of intracellular bacteria such as M. tuberculosis.
• Why not C? Eosinophils are not a major component of most granulomas, and they cannot destroy mycobacteria.
• Why not D? M. tuberculosis organisms reside in phagosomes, which are not acidified into phagolysosomes

3) A 4-year-old boy is exposed to Mycobacterium tuberculosis. A month later the child's tuberculin skin test is positive. The child then develops fever, and nonproductive cough. Which of the following findings is most likely to be present on the chest radiograph of this child?

A Hilar lymphadenopathy
B Miliary pulmonary nodules
C Pneumonic consolidation
D Upper lobe cavitation

Answer: A.

Explanation:
• The child has primary tuberculosis. Most healthy persons have subclinical disease, and a minority develop clinical manifestations; of those, most have limited pulmonary involvement without dissemination. Primary tuberculosis is marked by the Ghon complex, which is a small subpleural granuloma at mid- lung along with prominent enlarged hilar lymph nodes. These nodes may impinge upon central airways.
• Why not B? When the cell-mediated immune response is poor, then there can be numerous small granulomas scattered throughout the lungs, or disseminated to other organs, as a miliary pattern (granulomas that are the size of millet seeds).
• Why not C? Progressive primary tuberculosis can lead to more extensive lung involvement with pneumonic infiltrates.
• Why not D? Upper lobe cavitary disease is characteristic for secondary tuberculosis (reactivation or reinfection) in persons who have previously mounted an immune response.

Congratulations!
You've reached
the end of this sheet.