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PATHOLOGY

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TUBERCULOSIS

Tuberculosis is a communicable chronic granulomatous disease caused by Mycobacterium tuberculosis involving Lungs usually but may affect any organ.

Risk Factors

Flourishes under conditions of Poverty, crowding, and chronic debilitating illness.

The most common groups affected by TB is US:

■ older adults ■ the urban poor ■ patients with AIDS ■ and members of minority communities. ■ African Americans ■ Native Americans ■ the Inuit (from Alaska) ■ Hispanics ■ immigrants from Southeast Asia ■ diabetes mellitus ■ Hodgkin lymphoma ■ Chronic lung disease (particularly silicosis) ■ chronic renal failure ■ Malnutrition ■ Alcoholism ■ Immunosuppression ■ HIV

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

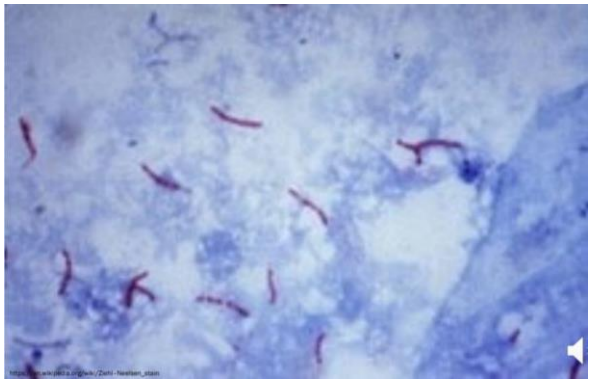
Etiology:

■ Mycobacteria:

– slender rods

– acid-fast (i.e., they have a high content of complex lipids that readily bind the Ziehl-Neelsen stain and subsequently stubbornly resist decolorization).

- The picture shows a Ziehl-Neelsen stain tissue section, there are cylindrical rods that are stained with purple color those are the bacilli of MTB.



M. tuberculosis hominis

■is responsible for Most cases of tuberculosis.

■ The reservoir of infection found in individuals with active pulmonary disease.

■ Transmission by:

– direct, by inhalation of airborne organisms in aerosols generated by expectoration

– exposure to contaminated secretions of infected individuals.

Mycobacterium bovis

– Oropharyngeal and intestinal tuberculosis

– contracted by drinking contaminated milk

- This type of TB is rare except in countries with tuberculose dairy cows and sales of unpasteurized milk which result in Oropharyngeal and intestinal tuberculosis.

Mycobacterium avium complex

■ Less virulent than M. tuberculosis

■ Rarely cause disease in immunocompetent individuals.

■ Cause disease in 10% to 30% of patients with AIDS.

Tuberculin (Mantoux) test:

■leads to Delayed hypersensitivity which can be detected by a test called tuberculin or mantoux test.

■ the test consist of intracutaneous injection of 0.1 mL of sterile purified protein derivative (PPD)

- The test is positive if it induces a visible and palpable induration at least 5mm in diameter that usually peaks within 48-72 hours.
- negative results you most likely have not been infected with a bacteria that causes TB, while positive test don't deffertiate between infection and disese.

■ A positive tuberculin skin test does not differentiate between infection and disease.

It is well recognized that the test has some limitations due to the presence of false negative and false positive reactions is some cases

■ False-negative reactions or skin test anergy can be related to:

– certain viral infections

– Sarcoidosis

– Malnutrition

– Hodgkin lymphoma

– immunosuppression

– overwhelming active tuberculous disease.

■ False-positive reactions may result from infection by atypical mycobacteria.

Infection vs. disease

It is important to know the difference between an infection and a disease

■Infection implies seeding of a focus with organisms. Which may or may not cause a clinically significant tissue damage

■ Disease is a clinically significant tissue damage

■ Routes of transmission mostly direct by P t P by:

  ■ Airborne droplets from active case to a susceptible host.

Pathogenesis

■ In the previously unexposed immunocompetent individual is centred on:

– Development of cell-mediated immunity

■ To resist the organism

■ To develop tissue hypersensitivity to tubercular antigens.

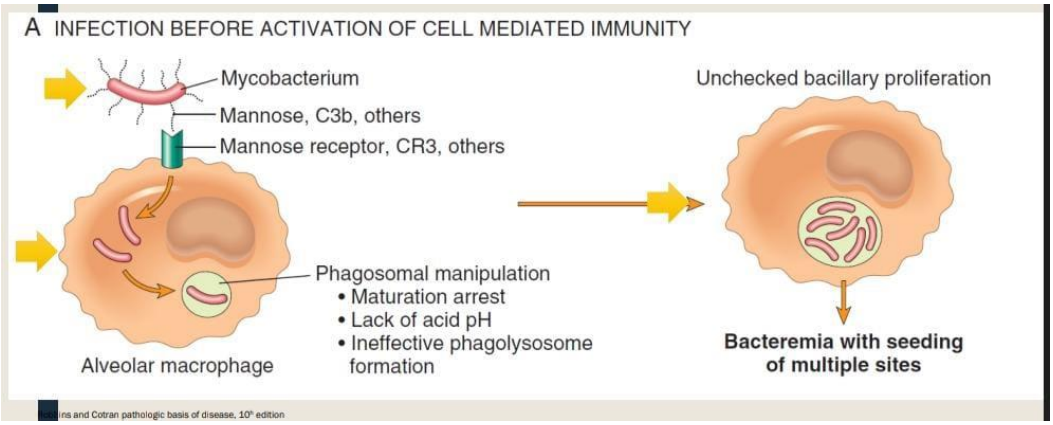
– Destructive tissue hypersensitivity as a part of the host immune responsible to the characteristic pathologic features of TB such as:

■ Caseating granulomas

■ Cavitation

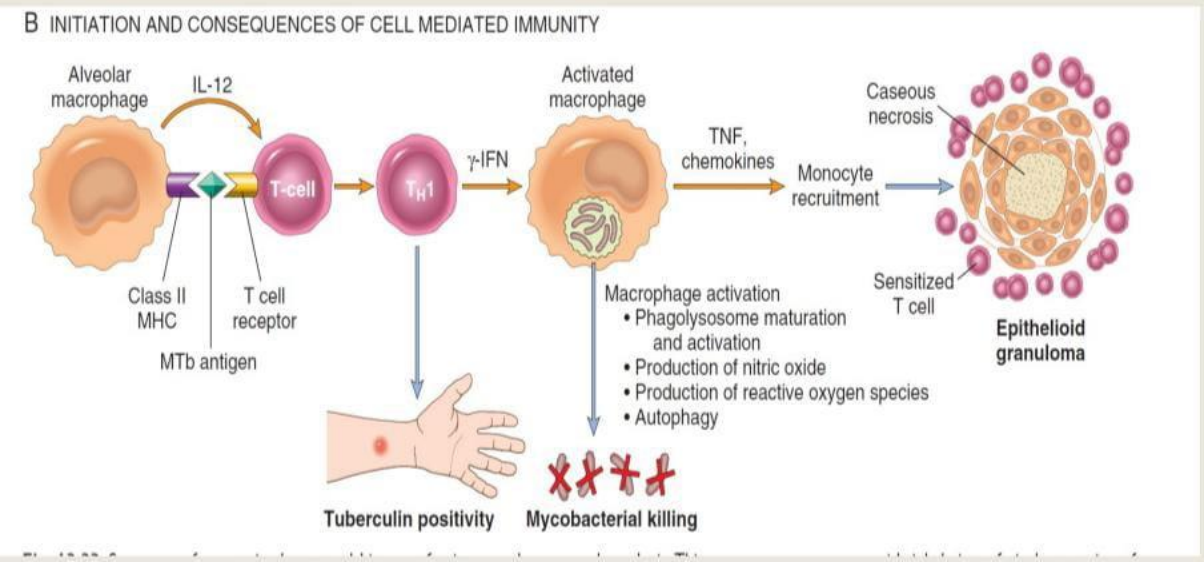
■ Acquisition of immunity to the organism.

Natural history of primary pulmonary tuberculosis



- Here, the first step in the history of primary pulmonary tuberculosis the sequence starts with inhalation of virulent strains of mycobacterium and the following step will follow within 3 weeks after exposure.
- 1st step is the entry of the virulent strains of Mycobacterium.
- 2nd step Entry into macrophages endosome, this process mediated by several macrophage receptors, including the macrophage mannose receptor and complement receptors that recognize several components of the mycobacterial cell walls.
- 3rd step Replication in macrophages, Once internalized, the organisms inhibit the macrophage's microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole allowing 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.



- this figure shows the sequence of events leading to the resistance of the organism and conversion to a positive results on a tuberculin skin testing.
- Development of cell mediated immunity (the following events take place approximately 3 weeks after exposure).

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

2nd - IFN-γ released by type 1 T helper cells is crucial in activating macrophages thus those Activated macrophages release a variety of mediators and upregulate expression of genes with important downstream effects, including:

I. TNF, which is responsible for recruitment activation and differentiation of monocytes into epithelioid histiocytes that characterize the granulomatous response.

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 mycobacterial organisms.

3rd Granulomatous inflammation and tissue damage→ Type 1 T helper lymphocytes (TH1) aid in the formation of granulomas and caseous necrosis.

- This response, in many individuals, halts the infection before significant tissuedestruction 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.

Activated macrophages

Release a variety of mediators and up-regulate expression of genes with important down stream effects as:

■ TNF

– Monocytes recruitment , activation and differentiation into the "epithelioid histiocytes" that characterize the granulomatous response

■ Inducible nitric oxide synthase (iNOS)

– raises nitric oxide (NO) levels, helping to create reactive nitrogen intermediates that are important in killing of mycobacteria

■ anti-microbial peptides (defensins)

- toxic to mycobacterial organisms.

Pathogenesis, Summary:

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

■ Immune response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue destruction

■ Defects in any of the steps of a TH1 T cell response (including IL-12, IFN-γ, TNF, or nitric oxide production)

– poorly formed granulomas

– absence of resistance

– disease progression.

Individuals with inherited mutations in any component of type 1 helper pathway are extremely susceptible to infection 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.

■ Hypersensitivity and resistance appear in parallel

– The loss of hypersensitivity (indicated by tuberculin negativity in a M.tuberculosisinfected patient) is an ominous sign of fading resistance to the organism. This can be indicated by tuberculin negativity in a mycobacterium MTB infected patients.

Primary Tuberculosis

■ mostly it is a self-limited Asymptomatic focus of pulmonary infection

■ Uncommonly may result in the development of fever and pleural effusions.

■ Viable organisms may remain dormant in **a tiny, telltale fibrocalcific nodule at the site of the infection** for several years (infection, not active disease) the only evidence of infection as it is asymptomatic.

These patients are infected but don’t transmit the organism to others.

■ If immune defenses are lowered, the infection may reactivate a potentially life threatening disease.

■ The form of disease that develops in a previously unexposed and therefore unsensitized patient.

■ 5% of newly infected acquire significant disease.

Primary Tuberculosis, presentation:

■ In otherwise healthy individuals:

– Mostly the only consequence are the foci of scarring. Which may harbor viable bacilli and serve as a nidus for disease reactivation at a later time if host defenses wane.

■ Uncommonly, new infection leads to progressive primary tuberculosis:

– Affected patients are:

■ overtly immunocompromised

■ have subtle defects in host defenses, (malnourished)

■ Certain racial groups, such as the Inuit

■ HIV-positive patients with significant immunosuppression

MORPHOLOGY

■ Almost always begins in the lungs.

■ The inhaled bacilli usually implant close to the pleura in the distal air spaces, typically close to the pleura

– in the lower part of the upper lobe

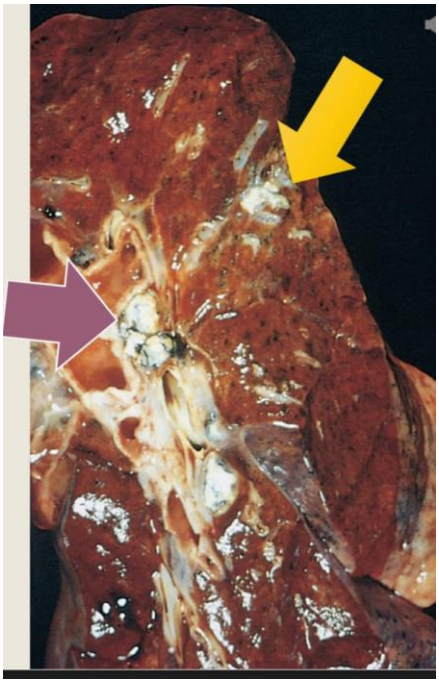
– in the upper part of the lower lobe.

MORPHOLOGY, grossly:

■ Ghon focus.

During the development of sensitization:

- ✓ a 1-cm to 1.5-cm area of gray-white inflammatory consolidation emerges during the development of sensitization
- ✓ in majority of cases the center of this focus undergoes caseous necrosis.



■ Tubercle bacilli, free or within phagocytes, travel via the lymphatic vessels to regional lymph nodes.

■ Ghon complex :This combination of parenchymal and nodal lesions.

- ➢ The yellow arrow points a gray white focus under the pleura in the lower part of upper lobe.
- ➢ The purple arrow points to higher lymph nodes that shows caseation.

■In the first few weeks, Lymphatic and hematogenous dissemination

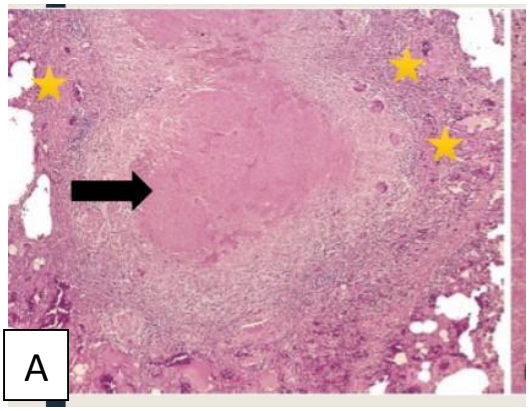
■ In 95% cell-mediated immunity controls the infection.

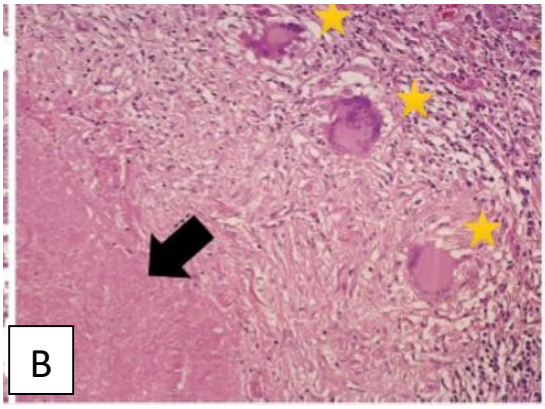
■ Ghon complex undergoes progressive fibrosis and calcification.

■ Despite seeding of other organs, no lesions develop.

MORPHOLOGY, microscopic:

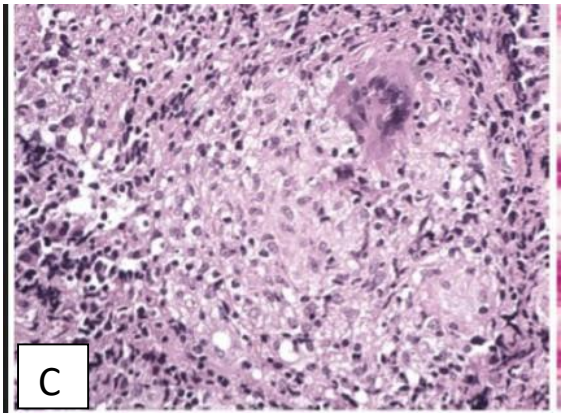
Histologically,sites of infection areinvolved by acharacteristic inflammatory reaction marked by the presence of caseating and non-caseating granulomas, which consist of epithelioid histiocytes and multinucleate giant cells. The figures show the morphologic spectrum of TB.

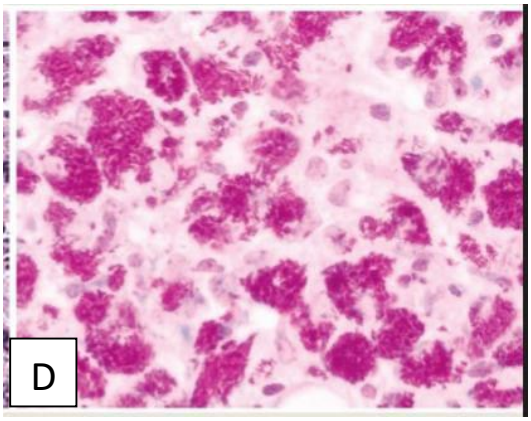




- Figure (A): characteristic tubercle at low magnification
- Figure (B): Same tubercle at higher magnification for the same focus.

The tubercle shows central granular caseation (black arrow) surrounded by epithelioid and multinucleate giant cells (yellow stars). 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)

■ Arises in a previously sensitized host when host resistance is weakened Or due to reinfection

■ <5% with primary disease develop secondary tuberculosis.

■ Secondary pulmonary tuberculosis:

- classically localized to the apex of one or both upper lobes.
- because of the pre-existence of hypersensitivity the bacilli excite a marked tissue response that tends to wall off the focus(localization)
- As a result of this localization regional lymph nodes are less involved early in the disease than they are in primary tuberculosis.
- On the other hand, cavitation leading to erosion into and dissemination along airways→important source of infectivity, because the patient now produces sputum containing bacilli.

MORPHOLOGY, grossly:

■ initial lesion is a small focus of consolidation,< 2 cm, within 1-2 cm of the apical pleura.

■ sharply circumscribed, firm, gray-white to yellow with variable amount of central caseation and peripheral fibrosis.

MORPHOLOGY, microscopic, histologically:

■ active lesions: coalescent tubercles with central caseation.

■ tubercle bacilli:

– can be demonstrated by appropriate methods in early exudative and

caseous phases of granuloma formation

– Impossible to find them in the late fibrocalcific stages.

■ Localized, apical, secondary pulmonary tuberculosis:

– heal with fibrosis either spontaneously or after therapy

– or may progress and extend along several different pathways.

■ progressive pulmonary tuberculosis:

– apical lesion enlarges with expansion of caseation area.

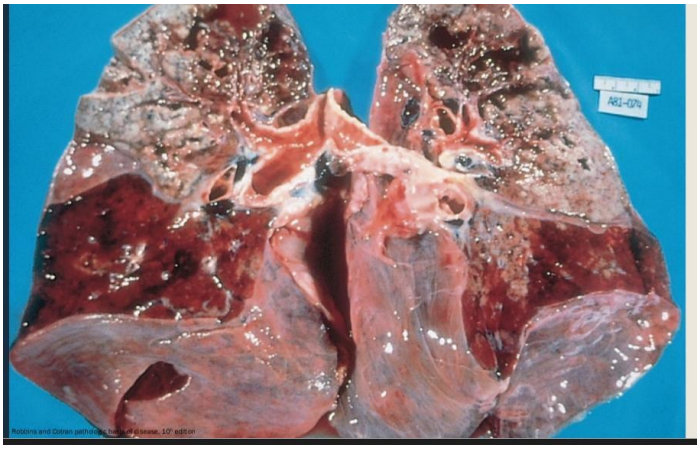
– Erosion into a bronchus evacuates the caseous center, creating a ragged, irregular cavity lined by caseous material that's poorly walled of by fibrous tissue.

– Erosion of blood vessels results in hemoptysis.

– With adequate treatment, the process may be arrested

– 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.

- The figure shows involvement of upper parts of both lungs by gray-white areas of caseation and multiple areas of softening in a patient with secondary pulmonary tuberculosis.



■ Miliary pulmonary disease :

–occurs when organisms reach the bloodstream through lymphatic vessels and then recirculate to the lung via the pulmonary arteries.

– the lesions are small (2-mm), yellow-white consolidation scattered through the lung parenchyma

– the word miliary is derived from the resemblance of these foci to millet seeds.

– With progressive pulmonary tuberculosis, the pleural cavity is invariably involved and serous pleural effusions, tuberculous empyema, or obliterative fibrous pleuritis develop.

– Endobronchial, endotracheal, and laryngeal tuberculosis may develop when the infective material is spread either through the lymphatic channels or from the expectorated infectious material.

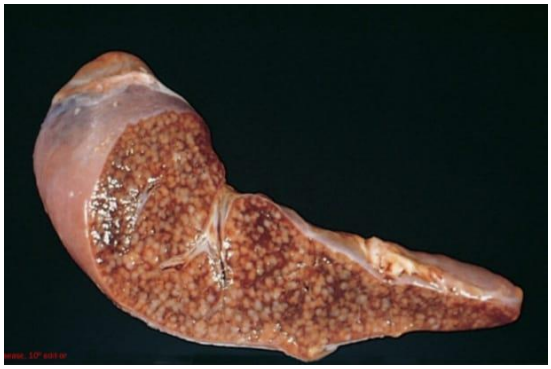
– The mucosal lining may show minute granulomatous lesions that can be seen only under the microscope.

■ Systemic miliary tuberculosis :

– when the organisms disseminate hematogenously throughout the body.

– It is most prominent in the liver, bone marrow, spleen, adrenal glands, meninges, kidneys, fallopian tubes, and epididymis.

- The figure shows military tuberculosis of the spleen, the cut surface shows numerous gray-white granulomas.



■ Isolated-organ tuberculosis:

– any organs or tissues seeded hematogenously and may be the presenting manifestation of tuberculosis.

– involve meninges (tuberculous meningitis), kidneys (renal tuberculosis),adrenal glands, bones (osteomyelitis), and fallopian tubes (salpingitis),

– vertebrae (Pott disease).

Lymphadenitis :

– the most frequent form of extrapulmonary tuberculosis

– usually involve cervical region

– unifocal, and most patients do not have concurrent extranodal disease.

– HIV-positive patients, have multifocal disease, systemic symptoms, and either pulmonary or other organ involvement by active tuberculosis.

Clinical Features

■ Asymptomatic especially in localized secondary tuberculosis

■ Insidious onset, with gradual development of both systemic and localizing symptoms and signs.

■ Systemic manifestations:

■ probably related to the release of cytokines by activated macrophages (mainly TNF and IL-1),

■ appear early in the disease course

■ include malaise, anorexia, weight loss, and fever.

■ Fever: low grade and remittent +/- night sweats.

– Pulmonary:

■ increasing amounts of sputum, at first mucoid and later purulent.

■ When cavitation is present, the sputum contains tubercle bacilli.

■ Hemoptysis (50%).

■ Pleuritic pain due to the extension of the infection into the plural surface.

– Extrapulmonary manifestations:

Depends on the organ system involved

■ infertility(fallopian tube), headache& neurologic deficits (meninges), back pain and paraplegia.

Diagnosis:

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

■ Ultimately, tubercle bacilli must be identified:

– The most common methodology for diagnosis of tuberculosis remains demonstration of acid-fast organisms in sputum by staining or by use of fluorescent auramine rhodamine. The most common

– Conventional cultures (requires up to 10 weeks),

– liquid media–based radiometric assays (give an answer in 2 weeks).

– PCR amplification on liquid media with growth, as well as on tissue sections, to identify the mycobacterium.

culture remains the standard diagnostic modality

as it can identify the occasional PCR negative cases and also allows testing for drug susptibility.

Prognosis :

■ determined by :

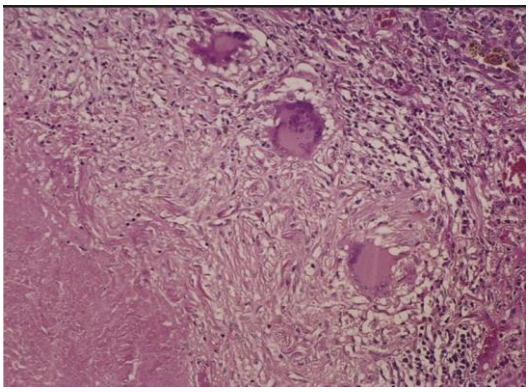
– the extent of the infection (localized versus widespread)

– the immune status of the host

– the antibiotic sensitivity of the organism

Now, try to solve the following ugly case ☹

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 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

The answer is A