

# Tuberculosis

- Tuberculosis is a communicable chronic disease

## Epidemiology

- It flourishes under conditions of poverty, crowding, in old people and disease states such as
  - a. Diabetes mellitus,
  - b. Hodgkin lymphoma,
  - c. silicosis
  - d. Immunosuppression..

## ***NOTE:***

- In areas of the world where HIV infection is prevalent, it has become the single most important risk factor for the development of tuberculosis

# Etiology

- 1- *M. tuberculosis hominis* is responsible for most cases of tuberculosis; the reservoir of infection typically is found in persons with active pulmonary disease
- Most infections are acquired by direct person to person transmission of airborne droplets of organisms from an active case to a susceptible host

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

## 2. Mycobacterium bovis

### a. Causes intestinal tuberculosis

- Is contracted by drinking milk contaminated with the microorganism
- infection is now rare in developed nations, but it is still seen in countries with tuberculous dairy cows and sales of unpasteurized milk.

- In years past, intestinal tuberculosis contracted by the drinking of contaminated milk was fairly common as a primary focus of tuberculosis.
- In developed countries today, intestinal tuberculosis is more often a complication of advanced pulmonary secondary tuberculosis, resulting from swallowing of coughed up infective material.

- The organisms are trapped in mucosal lymphoid aggregates of the small and large bowel, which then undergo inflammatory enlargement with ulceration of the overlying mucosa, particularly in the ileum



# PATHOGENESIS

- The pathogenesis in the previously unexposed immunocompetent person is centered on the development of a targeted cell mediated immunity that confers resistance to the organism and results in development of tissue hypersensitivity to tubercular antigens.

- The sequence of events from inhalation of the infectious inoculum

## **I. In the first 3 weeks**

- Once the mycobacteria gains entry into the macrophage endosomes , the organisms are able to inhibit normal microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole and this allows unchecked mycobacterial proliferation

- Thus, characterized by bacillary proliferation within the pulmonary alveolar macrophages with resulting bacteremia and seeding of multiple sites.
- Despite the bacteremia, most persons at this stage are symptomatic or have a mild flu-like illness.

## Note:

- The genetic makeup of the patient may influence the course of the disease.
- In some people with polymorphisms of the NRAMP1 (natural resistance associated macrophage protein 1) gene, the disease may progress from this point without development of an effective immune response.

- NRAMP1 is a transmembrane ion transport protein found in endosomes and lysosomes that is believed to contribute to microbial killing

## II. 3 weeks after exposure

- Development of cell-mediated immunity
  - a. Processed mycobacterial antigens reach the draining lymph nodes and are presented to CD4 T cells by dendritic cells macrophages and the macrophages secrete IL-12, that causes generation of TH1 subtype of CD4+ T cells that secrete - IFN which activates macrophages

b.. Activated macrophages, in turn, release a variety of mediators and upregulate expression of genes with important downstream effects, including

- (1) TNF, which is responsible for recruitment of monocytes, which in turn undergo activation and differentiation into the "epithelioid histiocytes"

- (2) expression of the inducible nitric oxide synthase (iNOS) gene, which results in elevated nitric oxide levels at the with excellent antibacterial activity;
- (3) generation of reactive oxygen species, which can have antibacterial activity



## Note:

- It is important that infection be differentiated from disease
  - Infection implies seeding of a focus with organisms, which may or may not cause clinically significant tissue damage (i.e., disease).

# Mantoux test

- Infection with *M. tuberculosis* typically leads to the development of delayed hypersensitivity, which can be detected by the tuberculin (Mantoux) test
- About 2 to 4 weeks after the infection has begun,

- Intracutaneous injection of 0.1 mL of PPD induces a visible and palpable induration (at least 5 mm in diameter) that peaks in 48 to 72 hours.
- A positive tuberculin skin test result
  - a. signifies cell-mediated hypersensitivity to tubercular antigens
  - b. It does not differentiate between infection and disease

- False-negative reactions (or skin test anergy)

- a. Certain viral infections,
- b. Sarcoidosis
- c. Immunosuppression
- d. Overwhelming active tuberculous disease

## False-positive reactions

- May result from infection by atypical mycobacteria

- About 80% of the population in certain Asian and African countries is tuberculin positive.
- In general, 3% to 4% of previously unexposed persons acquire active tuberculosis during the first year after "tuberculin conversion," and no more than 15% do so thereafter.
- Thus, only a small fraction of those who contract an infection develop active disease

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

# Primary Tuberculosis

- Is the form of disease that develops in a previously unexposed and so unsensitized patient.
- About 5% of those newly infected acquire the disease



- The inhaled bacilli implant in the alveoli of the of the lower part of the upper lobe or the upper part of the lower lobe, usually close to the pleura.
- As sensitization develops, (2-3 weeks after exposur) a 1-to 1.5- cm lesion develops (called Ghon focus ) composed of caseating granulomas

- Tubercle bacilli, travel in lymph drainage to the regional nodes, forming granuloma in the lymph nodes.
- The combination of Ghon focus and nodal involvement is called Ghon complex
- In approximately 95% of cases, development of cell-mediated immunity controls the infection

- The Ghon complex undergoes progressive fibrosis, followed by radiologically detectable calcification (Ranke complex)

- The major consequences of primary tuberculosis are that
  - (1) it induces hypersensitivity and increased resistance;
  - (2) The foci of scarring may harbor viable bacilli for years, perhaps for life, and thus be the nidus for reactivation at a later time when host defenses are compromised.

(3) uncommonly, it may lead to progressive primary tuberculosis and this complication occurs in patients who are immunocompromised or have nonspecific impairment of host defences, as characteristic in malnourished children or in elderly persons

- The incidence of progressive primary tuberculosis is particularly high in HIV-positive patients with an advanced degree of immunosuppression (i.e., CD4+ counts below 200 cells/ $\mu$ L).
- Immunosuppression results in an inability to mount a CD4+ T cell-mediated immunologic reaction that would contain the primary focus

- Because hypersensitivity and resistance are most often concomitant factors, the lack of a tissue hypersensitivity reaction results in the absence of the characteristic caseating granulomas (nonreactive tuberculosis)

Such persons are infected but do not have active disease and therefore cannot transmit organisms to others.

- When their immune defenses are lowered, the infection may reactivate to produce communicable and potentially life-threatening disease



# Secondary Tuberculosis (Reactivation Tuberculosis)

- Is the pattern of disease that arises in a previously sensitized host.
  - a. It may follow shortly after primary tuberculosis,
  - b. but more commonly it arises from reactivation of dormant primary lesions many decades after initial infection, particularly when host resistance is weakened.

c. It also may result from exogenous reinfection because of waning of the protection afforded by the primary disease

- Only a few patients with primary disease subsequently (5%) develop secondary tuberculosis.
- Secondary tuberculosis is classically localized to the apices of upper lobes related to high oxygen tension in the apices.

- Because of the preexistence of hypersensitivity, the bacilli excite a prompt and marked tissue response that tends to wall off the focus .
- As a result of this localization, the regional lymph nodes are less prominently involved early in the disease than they are in primary tuberculosis

- Cavitation occurs 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.

# CAVITATION





# CAVITATION AND CASEATION



- Secondary tuberculosis should always be an important consideration in HIV-positive patients who present with pulmonary disease
- Although an increased risk of tuberculosis exists at all stages of HIV disease, the manifestations differ depending on the degree of immunosuppression



1. Patients with CD4+ counts greater than 300 cells/mm present with "usual" secondary tuberculosis (apical disease with cavitations)

2. Patients with CD4+ counts below 200 cells/mm present with a clinical picture that resembles progressive primary tuberculosis (lower and middle lobe consolidation, hilar lymphadenopathy, and, no granulomas, and no cavitations (non-reactive disease).

## **Note**

- The extent of immunosuppression determines the frequency of extrapulmonary involvement, rising from 15% in mildly immunosuppressed patients to about 50% in those with severe immune deficiency

- The initial lesion usually is a small focus less than 2 cm within 2 cm of the apical pleura.
- Such foci have a variable amount of central caseation and peripheral fibrosis
- Erosion of blood vessels results in hemoptysis

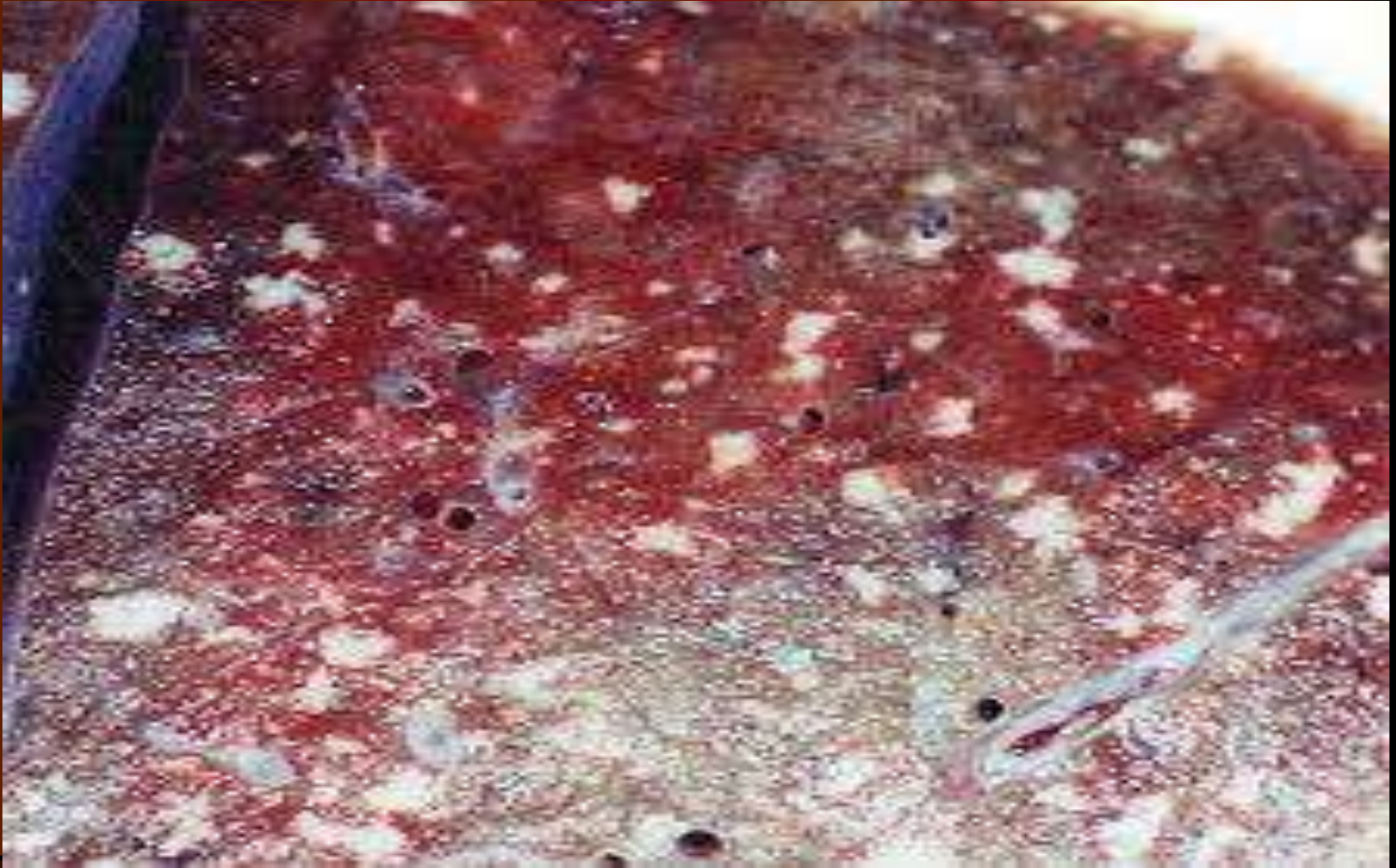
- With adequate treatment, the process may be arrested, although healing distorts the pulmonary architecture.
- If the treatment is inadequate, or if host defences are impaired, the infection may spread by direct expansion, by dissemination through lymphatic channels, or within the vascular system.

# 1. Miliary pulmonary disease

- Occurs when organisms drain through lymphatics into the lymphatic ducts, then empty into the venous return to the heart and then into the pulmonary arteries
- Individual lesions are small, (2 mm) foci scattered through the lung parenchyma



# Pulmonary MILIARY TB



## 2. Systemic miliary tuberculosis

- Occurs when the organisms disseminate through the systemic arterial system to almost every organ in the body.
- Is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis



### 3. Isolated-organ tuberculosis

- May appear in any one of the organs or tissues seeded hematogenously and may be the presenting manifestation of tuberculosis.

- Tuberculous involvement of Vertebrae is called (Pott disease).
- Paraspinal "cold" abscesses may track along the tissue planes to present as an abdominal or pelvic mass.

#### 4. Lymphadenitis

- Is the most frequent form of extrapulmonary tuberculosis, usually occurring in the cervical region ("scrofula").
- Usually focal
- In HIV patients: Multiple lymph nodes

# Clinical Features

- Localized secondary tuberculosis may be asymptomatic.
- If symptomatic, symptoms are insidious in onset.
- Systemic manifestations, include malaise, anorexia, weight loss, low grade fever, and night sweat

- With progressive pulmonary involvement, increasing amounts mucopurulent sputum
- Some degree of hemoptysis is present some cases of pulmonary tuberculosis.
- pleuritic pain

# Pulmonary Hypertension

- Pulmonary blood pressures are only about one eighth of systemic pressures.
- Pulmonary hypertension is one fourth of systemic levels
- Is most often secondary to:
  - a. a decrease in the cross sectional area of the pulmonary vascular bed,
  - b. or to increased pulmonary vascular blood flow.

I. Secondary type

II. Primary type



I. The causes of secondary pulmonary hypertension include:

1. Chronic obstructive or interstitial lung disease, which is accompanied by destruction of lung parenchyma and may consequent reduction in alveolar capillaries.
  - This causes increased pulmonary arterial resistance and secondarily, elevated arterial pressure.

## 2. Recurrent pulmonary emboli.

- Presence of these emboli leads to a reduction in the functional cross-sectional area of the pulmonary vascular bed, leading in turn to increased vascular resistance.

3. Antecedent heart disease, for example, mitral stenosis, which increases left atrial pressure, leading to higher pulmonary venous pressures, and ultimately pulmonary arterial hypertension

4 . Congenital left-to-right shunts

## II. Primary, or idiopathic, pulmonary arterial hypertension

1. The vast majority of cases are sporadic
2. 6% are familial with an autosomal dominant mode of inheritance

# PATHOGENESIS

- Pulmonary endothelial cell and/or vascular smooth muscle dysfunction is the probable underlying basis for most forms of pulmonary hypertension
  1. .In states of secondary pulmonary hypertension
    - endothelial cell dysfunction arises as a consequence of the underlying disorder due:

- a. To increased blood flow in left-to-right shunts,
- b. or biochemical injury produced by fibrin in recurrent thromboembolism

- Endothelial cell dysfunction reduces production of vasodilatory agents (e.g., nitric oxide, prostacyclin) while increasing synthesis of endothelin.
- There is production of growth factors and cytokines that induce the migration and replication of vascular smooth muscle and elaboration of extracellular matrix.

2. In primary pulmonary hypertension
  - a. In the uncommon familial form, the TGF- $\beta$  signaling pathway has emerged as a key mediator of endothelial and smooth muscle dysfunction., Specifically, germline mutations of bone morphogenetic protein receptor type 2 (BMPR-2), have been demonstrated in 50% of familial cases.



- It is a cell surface molecule that binds to a variety of TGF- $\beta$  pathway ligands,
- The BMPR2 gene product is inhibitory in its effects on proliferation; hence, loss of-function mutations of this gene result in abnormal vascular endothelial and pulmonary smooth muscle proliferation

- However, not all persons with germline mutations of BMPR2 develop primary pulmonary hypertension, suggesting the existence of modifier genes that probably affect penetrance of this particular phenotype

b. Sporadic forms of primary pulmonary hypertension

- There is a possible role for the serotonin transporter gene (5 HTT)
- Specifically, pulmonary smooth muscle cells from some patients with primary pulmonary hypertension demonstrate increased proliferation on exposure to serotonin

- Genetic polymorphisms of 5HTT that lead to enhanced expression of the transporter protein on vascular smooth muscle are postulated to cause their proliferation

# Morphology

1. in medium sized muscular arteries proliferation of myointimal cells and smooth muscle cells, causing thickening of the intima and media with narrowing of the lumina; and
2. in smaller arteries and arterioles thickening, medial hypertrophy, and reduplication of the internal and external elastic membranes

- In these vessels, the wall thickness may exceed the diameter of the lumen, which is sometimes narrowed to the point of near obliteration.

- Persons with idiopathic pulmonary arterial hypertension have characteristic **plexiform lesions**, in which endothelial proliferation forms multiple lumina within small arteries where they branch from a medium-sized artery

- Clinical Features

1. Secondary pulmonary hypertension develop at any age.
- The clinical features reflect the underlying disease, usually pulmonary or cardiac, with accentuation of respiratory insufficiency and right sided heart strain



## 2. Primary pulmonary hypertension,

- is almost always encountered in young adults,
- more commonly affect women,
- and is marked by fatigue, syncope (particularly on exercise), dyspnea on exertion.

- Eventually severe respiratory insufficiency and cyanosis develop
- Death usually results from right sided heart failure (decompensated cor pulmonale) within 2 to 5 years of diagnosis.

- Some amelioration of the respiratory distress can be achieved by vasodilators, and continuous prostacyclin infusions may prolong life (months to years),
- but without lung transplantation the prognosis is still grim