Lecture 9:

Tuberculosis

DEFINITION:

- communicable chronic granulomatous disease caused by Mycobacterium tuberculosis involving Lungs usually but may affect any organ.
- According to The World Health Organization (WHO) tuberculosis is considered as the most common cause of death resulting from a single infectious agent.
- Tuberculosis flourishes under conditions of poverty, crowding, and chronic debilitating illness.
- In the United States, tuberculosis is a much common in the following groups: like older adults, the urban poor, patients with AIDS, and members of minority communities, immigrants from Southeast Asia and Certain diseases such as diabetes mellitus, Hodgkin lymphoma, chronic lung disease (particularly silicosis), chronic renal failure, malnutrition, alcoholism, and immunosuppression. In areas of the world where HIV infection is prevalent, HIV infection is the dominant risk factor for the development of tuberculosis
- **Infection**: seeding of a focus with organisms, which may or may not cause clinically significant tissue damage
- **Disease**: means there is clinically significant tissue damage.
- **transmission**: acquired by direct person-to person transmission of airborne droplets of organisms from an **active case** to a susceptible host.

- **Primary tuberculosis**:
    - initial infection in a previously unexposed unsensitized patient.
    - self-limited asymptomatic focus of pulmonary infection
    - 5% **ONLY** of those newly infected acquire significant disease, uncommonly, may result in fever and pleural effusions.
    - Because it's asymptomatic the only evidence of infection, if any is a tiny telltale fibrocalcific nodule at the site of the infection. Viable organisms may remain dormant in such focus for several years and may be for the life of the host.
    - **Those individuals are infected but do not have active disease** and therefore cannot transmit organisms to others. But whenever their immune defenses are lowered, the infection may reactivate to produce communicable and potentially life-threatening disease.
    - usually in children.
    - In nearly all cases, these granulomas resolve and there is no further spread of the infection.

tuberculin (Mantoux) test:

- Infection with M. tuberculosis leads to delayed hypersensitivity reaction, which can be detected by at test called 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 that cause TB while positive test does not differentiate between infection and disease
- **test limitations:**
  - The false negative reactions can be related to certain viral infections, sarcoidosis, malnutrition, Hodgkin lymphoma, immunosuppression, and the presence of an overwhelming active tuberculous disease.
  - False positive reactions on the other hand may result from infection by atypical mycobacteria.

Etiology:

- **Mycobacteria:** slender rods acid-fast (which means they have a high content of complex lipids that bind the Ziehl-Neelsen stain and resist decolorization).
- **M. tuberculosis hominis**: responsible for most cases; the reservoir 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**: infection is contracted by drinking milk contaminated with *Mycobacterium bovis* . rare except in countries with tuberculous dairy cows and sales of unpasteurized milk. results in Oropharyngeal and intestinal tuberculosis
- **Mycobacterium avium complex:** less virulent than M. tuberculosis and rarely cause disease in immunocompetent individuals. responsible of TB in 10% to 30% of AIDS patients.

Pathogenesis:

- The pathogenesis of tuberculosis in previously unexposed immunocompetent individual is centered on the development of **cell-mediated immunity**
- cell-mediated immunity: resistance to the organism and development of tissue hypersensitivity to tubercular antigens.
- the destructive tissue hypersensitivity is responsible of characteristic pathologic features of tuberculosis, such as caseating granulomas and cavitation
- the natural history of primary pulmonary tuberculosis. (in the first 3 weeks after exposure)
  - inhalation of virulent strains of *Mycobacterium*
  - *entry of a* virulent strain of mycobacteria into macrophage endosome mediated by several macrophage receptors, including the macrophage mannose receptor and complement receptors that recognize several components of the mycobacterial cell walls.

- After entry the **organisms inhibit normal microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole,** allowing the mycobacterium to persist and proliferate.
- **during the earliest phase of primary tuberculosis (the first 3 weeks) in the nonsensitized patient a bacillary proliferation within the pulmonary alveolar macrophages and air spaces occurs, resulting in bacteremia and seeding of the organisms to multiple sites.** most individuals at this stage are asymptomatic or have a mild flulike illness.
- Under the influence of macrophage-secreted IL-12, type 1 T helper cells are generated and they start secreting IFN-γ.
- IFN-γ released by the 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:
  (1) TNF: recruitment of monocytes
  (2) inducible nitric oxide synthase (iNOS): which raises nitric oxide (NO) levels, helping to create reactive nitrogen intermediates which are important in killing of mycobacteria
  (3) anti-microbial peptides (defensins) that are also toxic to mycobacterial organisms.

- *3 wks after exposure cell-mediated immunity* is developed
- Granulomatous inflammation and tissue damage: Type 1 T helper lymphocytes aid in formation of granulomas and caseous necrosis, after being activated by IFN-γ, macrophages differentiate into the "epithelioid histiocytes" that aggregate to form granulomas; some epithelioid cells may fuse to form giant cells.
- In many individuals, this response 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, the Activated macrophages secrete TNF and chemokines, which promote recruitment of more monocytes.
- **immunity to a tubercular infection is primarily mediated by TYPE 1 Helper cells, which stimulate macrophages to kill mycobacteria.**
- This immune response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue destruction.
- 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.
- 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. This can be indicated by tuberculin negativity in a *M. tuberculosis*-infected patient

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:

- In countries in which bovine tuberculosis and infected milk have largely disappeared, primary tuberculosis almost always begins in the lungs.
- implant in the 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.

Ghon focus:

- During the development of sensitization, a 1-cm to 1.5-cm area of gray-white inflammatory consolidation emerges. This is called the **Ghon focus.** In the majority of 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**.
- Lymphatic and hematogenous dissemination to other parts of the body occurs during the first few weeks.
- The Development of cell-mediated immunity controls the infection in about 95% of cases. Therefore, the Ghon complex undergoes progressive fibrosis, and calcification.
- Despite seeding of other organs, no lesions develop.
- Histologically, sites of infection are involved by a characteristic inflammatory reaction marked by the presence of caseating and noncaseating granulomas, which consist of epithelioid histiocytes and multinucleate giant cells

Secondary tuberculosis:

- mostly in adults
- previously sensitized host by reactivation of previous infection particularly when health status declines or from reinfection.
- many decades after initial infection
- only a few patients with primary disease subsequently develop secondary tuberculosis.
- classically localized to the apex of one or both upper lobes.
- Localization: marked tissue response wall off the focus, resulting in less involvement of the regional lymph nodes especially if compared with primary tuberculosis.
- 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**.
- The initial lesion usually is a small focus of **consolidation**, less than 2 cm in diameter, within 1 to 2 cm of the **apical pleura.** sharply circumscribed, firm, gray, white to yellow areas that have a variable amount of central caseation and peripheral fibrosis. Histologically, the active lesions show characteristic coalescent tubercles with central caseation.

- The tubercle bacilli can be demonstrated in early exudative and caseous phases of granuloma formation, however it is usually impossible to find them in the late, fibrocalcific stages.
- heal with fibrosis either spontaneously or after therapy, otherwise the disease may progress.

progressive primary tuberculosis:

- Uncommon
- in patients who are overtly immunocompromised or who have subtle defects in host defenses, in malnourished individuals, Certain racial groups such as the Inuit, And HIV-positive patients with significant immunosuppression
- the apical lesion enlarges, and the area of caseation expands.
- 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.
- Erosion of blood vessels results in hemoptysis.
- With adequate treatment, the process may be arrested, although healing by fibrosis often results in distortion of the pulmonary architecture.
- 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.

Miliary pulmonary disease:

- occurs when organisms reach the bloodstream through lymphatic vessels and then recirculate to the lung via the pulmonary arteries.
- small lesions: foci of yellow-white consolidation scattered through the lung parenchyma
- *military:* resemble of foci to millet seeds

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

Isolated-organ tuberculosis: in any organ or tissue seeded hematogenously. Organs typically involved include the meninges, kidneys, adrenal glands, bones, and fallopian tubes. When the vertebrae are affected (Pott **disease).**

Clinically:

- the disease can be asymptomatic especially in Localized secondary tuberculosis.
- Systemic manifestations are related to the release of cytokines by activated macrophages (like TNF and IL-1), this often appears early in the disease course and include malaise, anorexia, weight loss, and fever. the fever commonly is low grade appearing late each afternoon and then subsides+/-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 tuberculosis.
- Pleuritic pain may result from extension of the infection to the pleural surfaces.

- Extrapulmonary manifestations of tuberculosis 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.
- tubercle bacilli must be identified by one of the following:
  1- demonstration of acid-fast organisms in sputum by staining or by use of fluorescent auramine rhodamine and this is considered The most common methodology for diagnosis of tuberculosis
  2- Conventional cultures for mycobacteria (requires up to 10 weeks)
  3- liquid media–based radiometric assays (within 2 weeks).
  4- PCR amplification.

culture remains the standard diagnostic modality because it can identify the occasional PCR-negative case and also allows testing of drug susceptibility.

Prognosis:

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