

## **PATHOGENESIS AND MORPHORLOGY OF TUBERCULOSIS**

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### **INTRODUCTION**

Tuberculosis is the second leading infectious cause of death in the world after HIV, affecting 1.7 billion people worldwide and killing 1.7 million each year.

Most cases of TB are caused by *M. Tuberculosis* and the reservoir of infection is humans with active TB. Most cases of TB are pulmonary and acquired by person to person transmission of air-borne droplets of organisms. Oropharyngeal and intestinal TB contracted by drinking dairy milk contaminated with *M. Bovis* rarely seen nowadays and usually in countries with tuberculous dairy cows and unpasturised milk.

Infection with *M. tuberculosis* is different from disease. Infection which is the presence of the organism may or may not cause clinically significant disease.

Viable organisms may remain dormant for decades until immunity is suppressed, infection may then be reactivated to produce disease.

### **PATHOGENESIS AND MORPHORLOGY OF TUBERCULOSIS**

The sequence of events/pattern of host response following an infection depends on the state of host immunity and whether the infection represents a

primary exposure to the organism or secondary reaction in an already sensitized host.

### **Primary Infection**

Primary infection with *M. Tuberculosis* begins with inhalation of the organism and ends with a T-cell mediated immune response that controls the infection in 95% of cases. Inhaled *M. Tuberculosis* is endocytosed by alveolar macrophages by binding lipoarabinomannan on the bacterial cell wall through mannose receptors and binding opsonized mycobacteria through complement receptors. At this point the macrophages are naïve and unable to kill mycobacteria which multiply, lyse the host cell, infect more macrophages and through them reach the hilar lymph nodes. Live bacteria prevent phagolysosome fusion by mechanisms including inhibition of  $Ca^{2+}$  signals and blockage of recruitment and assembly of proteins mediating phagolysosome fusion. Dissemination through the blood to other parts of the lungs and body may occur at this stage. A T-cell mediated immunity demonstrable by a positive purified protein derivative test reaction usually develops at about 3wk post infection This T helper 1 (TH1) response activates macrophages to become bactericidal.

This TH1 response is stimulated by mycobacterial antigens draining to Lymph Nodes and presented by Antigen Presenting Cells which produce IL-12 that causes the differentiation of TH1 cells. Activation of T-cells leads to the following

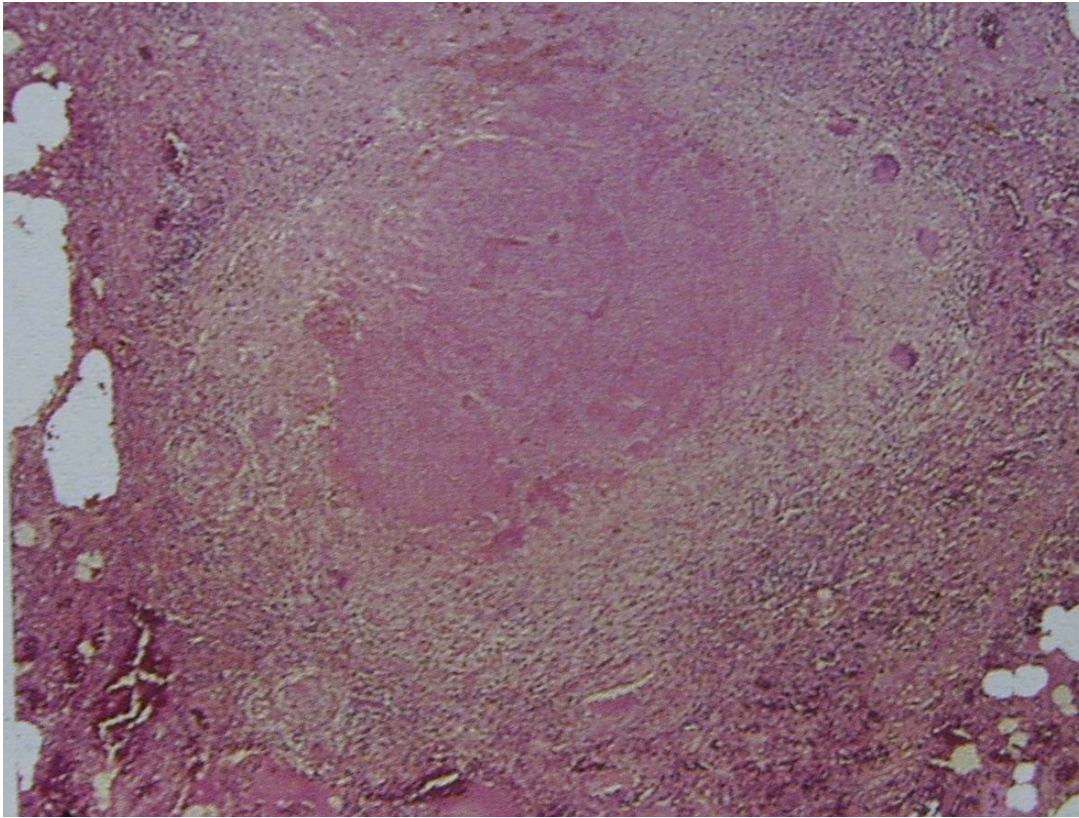
- CD4<sup>+</sup> T cells secrete IN $\gamma$  to activate macrophages leading to epitheloid cell and granuloma formation and killing of intracellular mycobacteria through reactive Nitrogen Intermediates (NO,NO<sub>2</sub>,HNO<sub>3</sub>)
- CD8<sup>+</sup> T cell lysis of infected macrophages with killing of mycobacteria this process is Fas independent, granule dependent
- CD4<sup>-</sup>CD8<sup>-</sup> T cells lyse macrophages without killing bacteria (Fas dependent).

Lysis of the macrophages results in the formation of caseating granulomas. mycobacteria being unable to grow in this acidic extracellular anaerobic environment are thus contained.

### Morphology

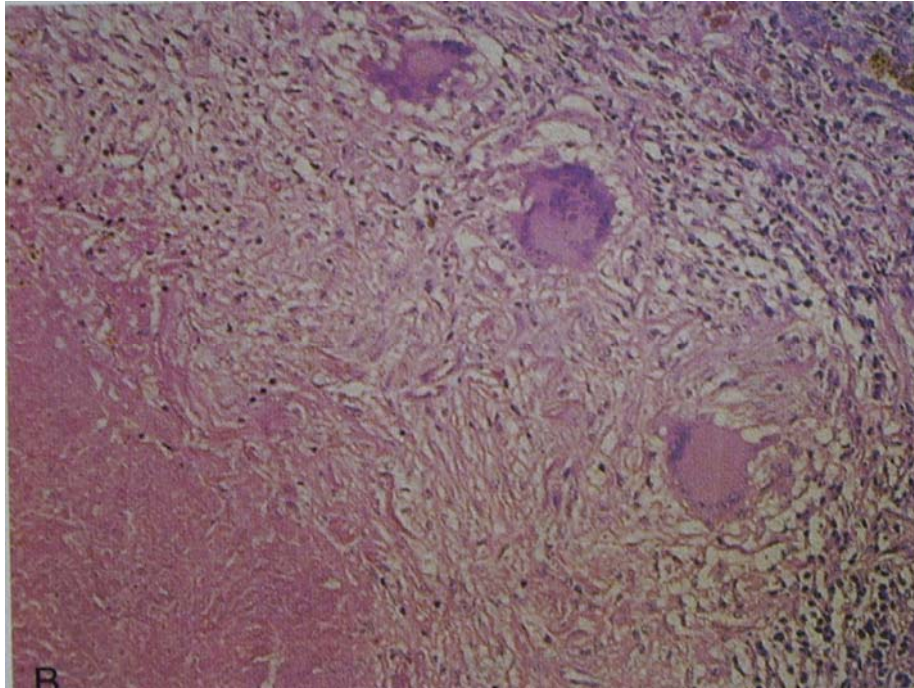
Generally the only evidence of infection that remains if any is a tiny fibrocalagic scar at the site of healed infection. Active lesions are seen as characteristic granulomatous inflammatory reaction that form caseating (**Figs: I and II**) and non caseation tubercles (**Fig: III**). Individual tubercles are microscopic but may coalesce to become macroscopically visible.

**Fig I. CASEATING TUBERCLE**





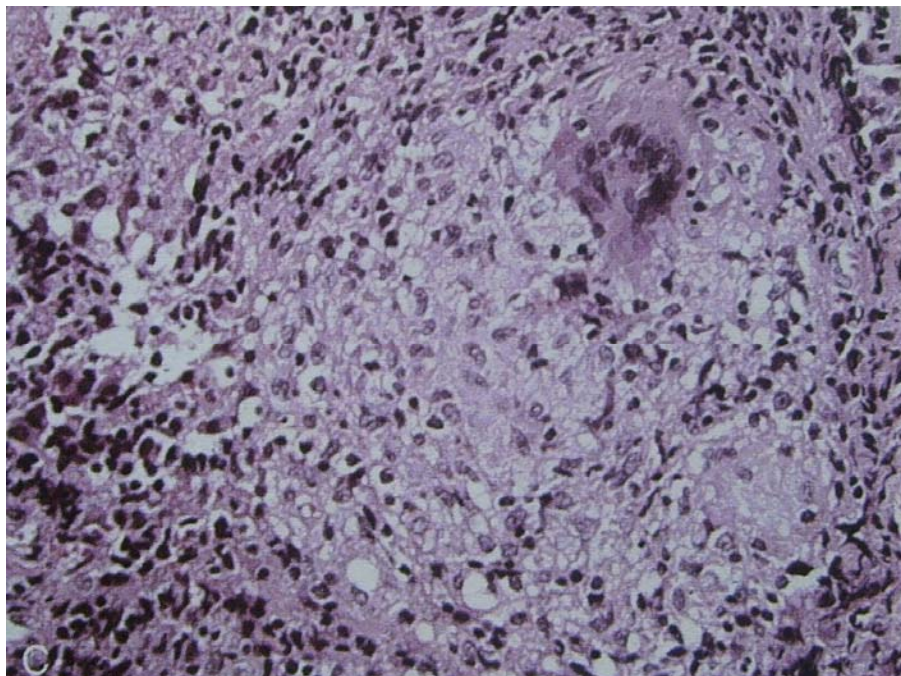
**Fig II: CASEATING TUBERCLE**



Granulomas are an accumulation and epithelioid macrophages arranged in small clusters or nodular collections surrounded by a fibroblastic rim

punctuated by lymphocytes. some the macrophages form giants cells and in TB a central area of caseating necrosis is characteristically seen **Fig 1.**

**Fig III: NON-CASEATING TUBERCLE**



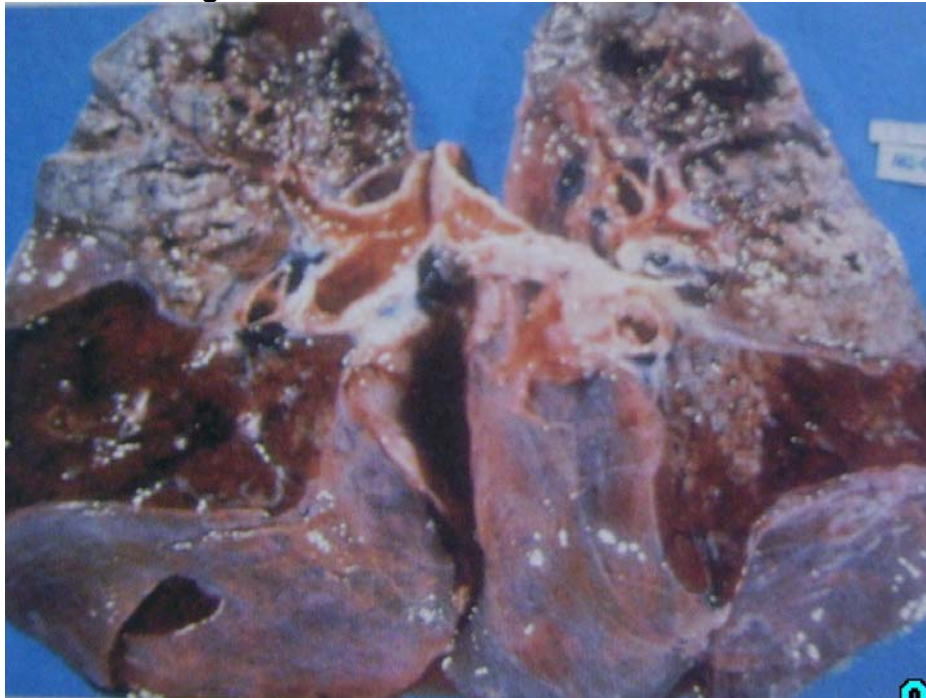
## SECONDARY AND DISSEMINATED TB

This occurs as a result of a reinfection, reactivation of dormant disease or direct progression of a primary TB into disseminated disease. This may be due to increased susceptibility of the host to disease or to a particularly virulent strain of mycobacteria.

Granulomas of secondary TB are found most often in the lung apices or

may be disseminated in the lungs, kidneys, meninges, marrow and other organs. These granulomas that fail to contain mycobacterial infection are the major cause of tissue damage in secondary TB. Cavities are a common feature of 2<sup>o</sup> TB. Necrosis may rupture into vessels or airways spreading mycobacteria throughout the body or releasing them in aerosols.

**Fig IV: SECONDARY PULMONARY TB**



### MORPHOLOGY OF SECONDARY TB

Secondary TB may take any of many forms. In all, granulomas are seen in the organs or at sites involved. Initial lesion is usually a small area of consolidation at the lung apex. Progressive pulmonary TB, common in elderly or immunocompromised, occurs as an expansion of apical lesion (**Fig IV**) with expansion of area of caseation erosion into bronchus evacuates the caseous center leaving a cavity.

- ▶ miliary pulmonary TB occurs as a consequence of lymphatic drainage ultimately to the right

heart, then to pulmonary arterial circulation producing microscopic or millet seed lesions throughout the lungs. Pleural effusion, tuberculous empyema and tuberculous fibrous pleuritis may develop.

- ▶ Endobronchial, endotracheal, laryngeal TB
- ▶ Systemic miliary TB- liver, bone, adrenals, spleen (**Fig. V**), kidneys, meninges
- ▶ Isolated organ TB
- ▶ Lymphadenitis – usually unifocal
- ▶ Intestinal TB – mucosal ulceration



**Fig IV: MILIARY TB OF THE SPLEEN**



**MYCOBACTERIUM AVIUM INTRACELLULARE COMPLEX.**

The 3 subspecies of Mycobacterium Avium and Mycobacterium Intracellulare cause similar infections and are simply referred to as Mycobacterium Avium Intracellulare Complex or MAC. Clinically significant infection is only common among people with AIDS and low CD4+ T LYMPHOCYTES (<60CELLS/mm<sup>3</sup>)

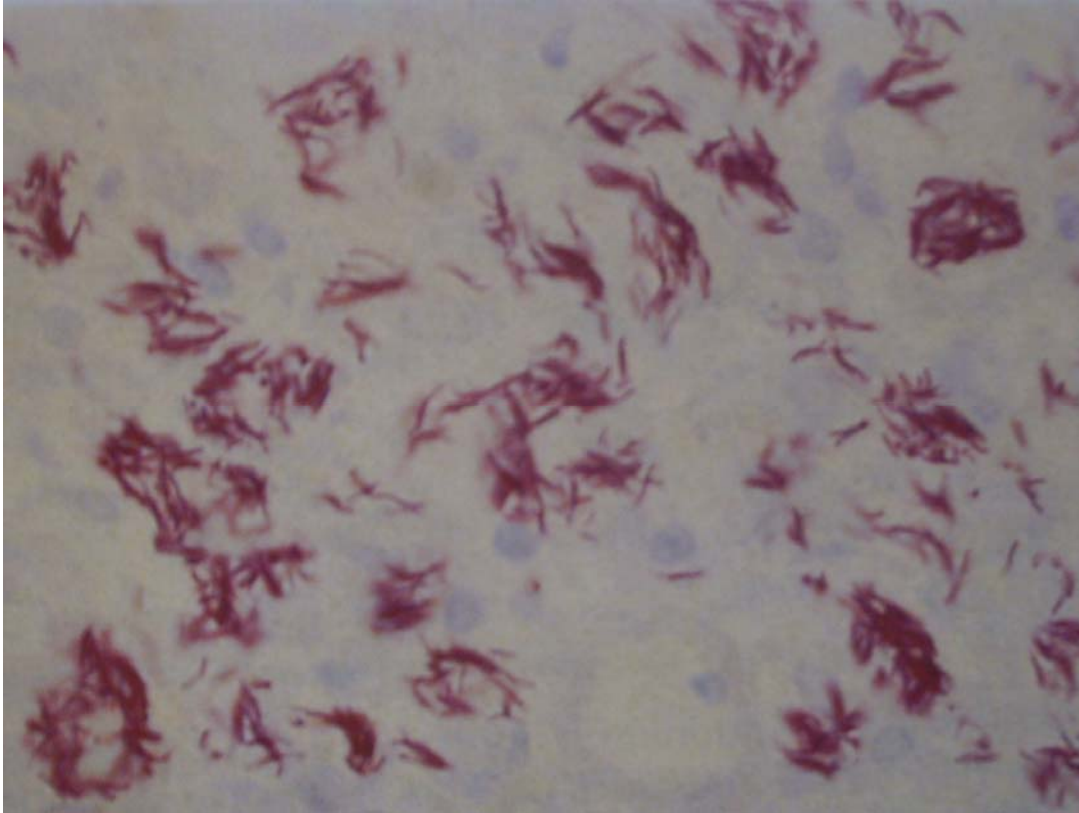
Disseminated disease with high levels of organisms is seen in AIDS. Patients are feverish, lose weight and have drenching night sweats.

Rarely in patients without HIV, MAC infection occurs and presents primarily as a pulmonary infection with productive cough and weight loss.

**Morphology**

Widely disseminated infection affecting lymph nodes, liver and spleen. Organ may have a yellow tinge due to abundant organisms in tissue macrophages. Microscopically abundant acid-fast bacilli are seen within macrophages (**Fig. VI**). Granulomas, lymphocytes and tissue destruction are rare.

**Fig VI: ABUNDANT ACID-FAST BACILLI IN MACROPHAGES**



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