

# PATHOLOGY OF MYCOBACTERIAL INFECTION IN DIABETES

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## INTRODUCTION

Tuberculosis is at least as old as mankind and the history of tuberculosis is intertwined with that of civilization. Over the centuries its prevalence has waxed and waned but it remained a continuous threat. Its association with diabetes mellitus was reported by Avicenna (Ibn Sina 980-1037) an Arabian physician [1,2]. It was the leading cause of death in diabetic patients in the preantibiotic era and more than 50% of them were documented to have had pulmonary tuberculosis during postmortem examination[2].

Root [3] studied 245 cases of associated diabetes and tuberculosis in 1934 and made the following observations:

- a. development of tuberculosis in juvenile diabetics occurred ten times more frequently than amongst non-diabetic patients
- b. development of tuberculosis followed the onset of diabetes in 85% cases.
- c. incidence of pulmonary tuberculosis increased with the duration of diabetes mellitus.

Various theories were put forward to explain the increased incidence and the pathogenesis of tuberculosis in diabetes, such as: hyperglycemia, acidosis, low opsonic index, decreased bactericidal activity, hypovitaminosis and increased availability of glycerol. These will be dealt in some detail later.

## PATHOGENESIS [4,5,6,7,8]

Three important aspects in the pathogenesis of tuberculosis are:

1. Virulence of the organism (presence and multiplication)
2. Hypersensitivity vs immunity against infection
3. Tissue destruction and caseous necrosis

The tubercle bacilli have no known exotoxins, endotoxins or histolytic enzymes. Their pathogenicity is due to their ability to escape killing by macrophages and to induce delayed type of hypersensitivity.

The components of the mycobacterial cell wall responsible for the virulence are :

- a. Cord factor
- b. Sulfatides
- c. LAM (lipoarabinomannan B)
- d. M. tuberculosis heat-shock protein
- e. Complement.

Tuberculosis in man is mainly caused by Mycobacterium tuberculosis, which is commonly transmitted by droplet nuclei of 1 to 5 µm size.

The primary phase of tuberculosis begins with inhalation of tubercle bacilli and ends with a T cell-mediated response (when a positive PPD test develops) that includes hypersensitivity to the organisms and controls 95% of infections. The pattern of host response depends on whether the infection represents a primary, first exposure to the organism, or secondary reaction in an already sensitized host.

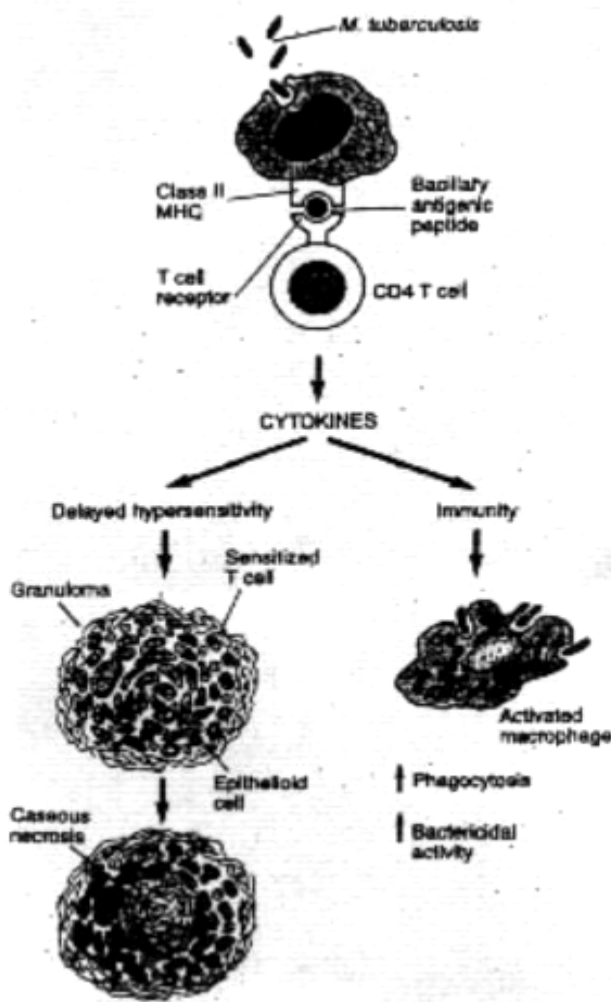
The first infection with the tubercle bacillus is known as primary tuberculosis, in which the draining lymph nodes are also involved and the combination is known as the 'primary complex'. Tuberculosis most frequently involves the lung. The other primary sites are cervical lymph nodes, intestinal tract and skin. Though the oral route of entry was common earlier, due to consumption of infected milk resulting in tonsillar and intestinal lesions, currently in majority of the cases infection is by inhalation, causing pulmonary tuberculosis.

The primary lesion is subpleural. When the bacilli are in an alveolus, serous or serofibrinous exudate containing neutrophils occurs for a short duration, after which macrophages take up the role of phagocytosis. The subpleural lesion just above or below the interlobar fissure, between upper and lower lobes of the lung, is known as "Ghon focus". It is a yellow-white, softened area of 10 to 20 mm diameter, comprising of fibrinous exudate, numerous acidfast bacilli and granulation tissue

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around. The tubercle bacilli can be destroyed or inhibited, or they can multiply. The subsequent course is determined by the immune response. The macrophages containing the bacteria are transported to hilar nodes. These macrophages sensitize T cells by presenting antigens. The macrophages in the alveoli are lysed by multiplying tubercle bacilli. The latter infect other macrophages and at this stage, spread of bacilli to other parts of the lung as well as the body can take place. After two to three weeks, T cell-mediated immunity develops. T cell and macrophage interactions are important. T cells are sensitized by macrophages through monokines. T cells, through lymphokines interact with macrophages in two way (Fig 1).



**Fig. 1: Macrophage : activation and sensitization in tuberculosis**

1. CD4 + helper T cells secrete interferon-gamma which activates macrophages and the activated macrophages in turn develop bacterial function via reactive nitrogen intermediates (NO, NO<sub>2</sub> and HNO<sub>3</sub>) which kill the intracellular mycobacteria. This is associated with the

formation of epithelioid cell granuloma and clearance of mycobacteria.

2. CD8+ suppressor T cells kill macrophages which are infected with bacilli, resulting in the formation of 'caseating' granuloma. This delayed type hypersensitivity (Type IV) to the tubercle bacillus probably explains the organism's destructiveness in tissues and also the emergence of resistance to the organisms.

The presence of poorly digestible particles of tubercle bacilli and/or T cell-mediated immunity to the irritant are necessary for the formation of granulomas. As mentioned earlier, interferon-gamma elaborated by T cells is responsible for transforming macrophages into activated macrophages (epithelioid cells and giant cells). In tuberculous granulomas, more CD4+ cells are seen in the centre and the periphery shows CD8+ cells, epithelioid cells and B cells.

Mycobacteria can not grow in acidic extracellular environment lacking in oxygen and hence the infection is controlled. The end result is calcified lesion in the lung and in the hilar node.

After resolution of the primary infection, small numbers of bacilli survive within the scarred foci for many years. The majority, 90% to 95% do not progress further.

Lurie, quoted by Sheffield (9) classified pathogenesis of tuberculosis into four stages:

Upto 2 to 4 weeks,

Stage I – Earlier reaction by neutrophils Later by macrophages.

Stage II -- Bacillary multiplication in macrophages  
Macrophage death  
Recruitment of monocytes.

State III – Transportation of bacilli to lymph nodes  
Granuloma formation

Following reactivation,

Stage IV – Marked caseous / liquefactive necrosis with extracellular multiplication of tubercle bacilli.

Secondary tuberculosis is caused by the reactivation of the disease. This occurs when the host resistance is impaired, which may be due to immunosuppression from any cause, including malnutrition, alcoholism, malignant disease, silicosis, acquired immune deficiency syndrome (AIDS) and diabetes mellitus [9].

## **FACTORS RESPONSIBLE FOR PATHOGENESIS OF TUBERCULOSIS IN DIABETES MELLITUS**

It was observed that the lowering of natural resistance was an important factor for increased incidence of tuberculosis in diabetes [10]. Alterations in the biochemical conditions in blood and tissues, and decreased antibody formation result in lowered resistance [11]. Experimentally, it was shown that dogs lost their natural resistance to tuberculosis after pancreatectomy and the resistance of albino rats lowered after inducing hypoerglycemia. The tubercles in this situation were more confluent, widespread and richer in bacilli than among the controls. Long and Vorwald, quoted by Pagel [10], had shown that increased availability of glycerol may be responsible for multiplication of bacilli in the tissues of diabetics. Pagel noted that in diabetes, pulmonary tuberculosis showed special features like large confluent lesions which tend to liquefy extensively.

Malnutrition plays a role in the lowering of metabolic activity of macrophages and interleukin-1 production, thereby leading to the progress of disease [6]. In addition, hepatic dysfunction with demonstrable depletion of glycogen and consequent hypovitaminosis may play a major role in the causation of tuberculosis in diabetic patients [11].

Kass [12] reported that pituitary dysfunction increased the susceptibility to tuberculosis. Overproduction of adrenocorticotrophic hormone (ACTH) and consequent rise in corticosteroids may result in enhanced exudative inflammatory response but retarded granulation tissue formation.

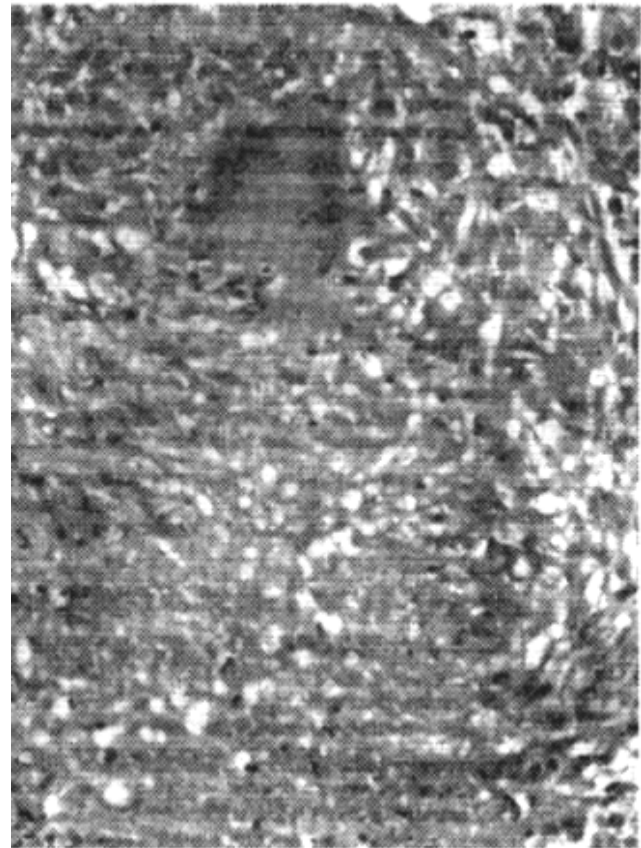
Erokhin and Gedymin [13] observed defective defence mechanisms of alveolar macrophages, type II alveolocytes and fibroblasts in the lungs of patients with tuberculosis and diabetes mellitus.

Tsukaguchi et al [14] measured the production of interleukin-1 beta (IL-1beta), tumor necrosis factor alpha (TNF alpha), and interleukin-6 (IL-6) by peripheral monocytes of patients with pulmonary tuberculosis and diabetes, and observed that the cytokine production was significantly impaired in these patients, suggesting a close correlation between tuberculosis immunity and diabetes.

## **LIGHT MICROSCOPIC APPEARANCE OF GRANULOMA [4,9,15]**

The hall mark of the infection is the caseating epithelioid cell granuloma, also known as 'tubercle'. The granuloma prototype or non-caseating tubercle

is composed of a focus of epithelioid cells rimmed by fibroblasts, lymphocytes, histiocytes and an occasional Langhans' giant cell. A caseating tubercle is characterized by central amorphous granular debris with no cellular detail (caseous necrosis) and variable number of acidfast bacilli. The necrotic zone is surrounded by epithelioid cells, lymphocytes and Langhans' giants' cells (Fig 2 ). The granulomas can be discrete or coalescent. Older granulomas develop an enclosing rim of fibroblasts and connective tissue. Caseous necrosis is a distinctive form of coagulative necrosis, grossly white and cheesy, enclosed within granulomatous reaction. The amount of caseation is dependent on the sensitization of the patient and the virulence of the organisms. The epithelioid cells are large, having abundant pale eosinophilic granular cytoplasm with indistinct cell boundaries and oval or elongate vesicular nuclei sometimes with folded nuclear membrane. The lymphocytes are mostly sensitized T cells which elaborate lymphokines. The Langhans' giant are formed by fusion of epithelioid cells, measure 40 to 50 mm in diameter and contain large amount of eosinophilic cytoplasm with 20 or more peripherally arranged small nuclei.



*Fig. 2: Tuberculosis granuloma showing caseous necrosis rimmed by epithelioid cells, lymphocytes and a Langhans giant cell.*

The presence of Langhans' giant cell is only a sign of chronicity.

### **ELECTRON MICROSCOPIC APPEARANCE OF EPITHELIOID CELL [9]**

The epithelioid cell shows deeply indented nucleus with dense nuclear chromatin and a prominent nucleolus. Numerous mitochondria are seen. The other cell organelles include strands of rough endoplasmic reticulum, lysosomes, microfilaments and microtubules. Prominent cytoplasmic vacuoles containing fluffy homogeneous material are characteristic of epithelioid cells. Presence of rough endoplasmic reticulum and Golgi lamellae suggest that the epithelioid cell is changing from predominantly phagocytic to secretory form. In addition, these cells are interconnected by cytoplasmic projections. The intercellular junctions provide cell-to-cell communication. Also, adhesion molecules are associated with these junction complexes.

### **PATHOLOGY OF TUBERCULOSIS [9,15,16]**

Morbid anatomy of tuberculosis depends on the complex interrelationship between tubercle bacilli and immunity versus hypersensitivity of the host. The manifestations are influenced by local blood flow and oxygen/carbon dioxide concentration. Except for severity of tuberculous lesions in some cases, no histologic features are characteristic in patients of diabetes mellitus. The appearances of tuberculous granulomas have been mentioned earlier.

A brief outline of tuberculous lesions is given below.

#### **Primary pulmonary tuberculosis**

- Ghon complex (primary focus) heals completely with or without calcification in 90% of cases.
- Dormant foci can get reactivated later giving rise to postprimary (secondary) tuberculosis.
- Primary lesion may become progressive and merge directly into postprimary tuberculosis.
- Hematogenous spread results in miliary tuberculosis and tuberculous meningitis. Chronic forms include tuberculosis of kidneys, bones, joints etc.

#### **Postprimary pulmonary tuberculosis**

This can arise in four ways :

1. Direct progression of primary lesion.
2. Reactivation of a dormant primary lesion.
3. Hematogenous spread to lungs.
4. Exogenous superinfection.

Most of the cases occur as a result of direct progression or reactivation. Variety of histologic types of lesions are produced which may vary from patient to patient and within the same lung.

The histologic lesions are :

- a. Pre-exudative
- b. Exudative
- c. Caseating
- d. Profective
- e. Regressive
- f. Fibrotic
- g. Calcified
- h. Ossified: The tubercle bacilli gradually diminish in number as the lesions get sclerotic or calcified.
- i. A progressive lesion is one in which the caseous material becomes liquefied and formation of cavity takes place. The wall of the cavity is usually lined by softened caseous material containing numerous bacilli. Scanty productive lesions and rim of fibrous tissue are seen around its periphery. Surrounding the cavity, atelectatic areas are observed.

Spread of tuberculosis can result in the following.

- Bronchi – Endobronchial tuberculosis and ulceration
- Bronchial arteries – Bronchiectasis, cold abscess
- Pulmonary arteries – Decreased pulmonary function
- Pulmonary veins – Dissemination to all parts of the body
- Pleura – Tuberculous empyema

## Extraopulmonary tuberculosis

The common sites of spread are lymph nodes, eye, bones, joints, liver, spleen, kidneys, adrenals, prostate, seminal vesicles, fallopian tubes, endometrium, and meninges.

Isolated tuberculous infection can occur in cervical lymph nodes, meninges, kidney, adrenals, bones, uterine tubes and epididymis.

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