بسم الله الرحمن الرحيم

DISEASES OF THE RESPIRATORY SYSTEM 2017
DR HEYAM AWAD
LECTURE 7: TUBERCULOSIS

Reference:

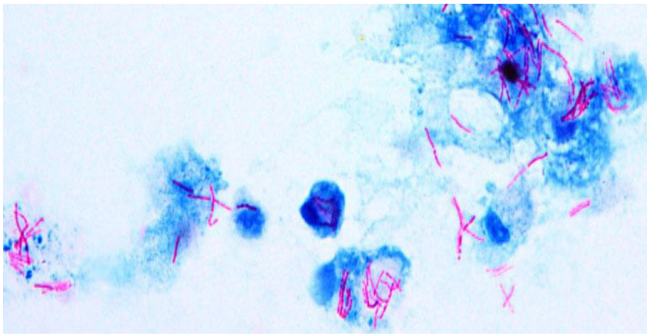
Robbins 9th: page: 493-499 10th: page : 526-532

TUBERCULOSIS

Tuberculosis is a communicable chronic disease caused by mycobacterium tuberculosis which **are acid fast bacilli**. It usually involves the lungs but it can affect other organs in the body.

Acid-fastness is a physical property of certain bacterial and eukaryotic cells making them resistant to decolorization by acids during laboratory staining procedures.

The most common staining technique used to identify acid-fast bacteria in the Ziehl-Neelsen (ZN) stain (pic below), in which the acid-fast species are stained bright red and stand out clearly against a blue background.



Note: It is important that TB infection be differentiated from disease: infection implies seeding of a focus with organisms, which may or may not cause clinically significant tissue damage . the presence of tissue damage is what is considered a disease.

Epidemiology

TB flourishes under conditions of poverty, crowding, in old people and disease states such as Diabetes mellitus, Hodgkin lymphoma, Silicosis and Immunosuppression, including AIDS.

The incidence of TB declined but it is increasing nowadays due to increased HIV infection.

According to WHO statistics: Tuberculosis (TB) is one of the top 10 causes of death worldwide. In 2016, 10.4 million people fell ill with TB, and 1.7 million died from the disease (including 0.4 million among people with HIV). Over 95% of TB deaths occur in low- and middle-income countries.

In Jordan, newly diagnosed TB cases must be reported to the ministry of health. The table below is from the ministry of health website and shows the number of cases diagnosed with TB.

حالات التدرن الرئوي و غير الرئوي المكتشفة خلال الاعوام

من السنة :2000 الى 2016

السنة	التدرن الرئوي			التدرن غير الرئوي		المجموع الكلي	نسبة الحدوث للنوعين لكل 100.000
	العدد	ايجابي القشع	نسبة ايجابي القشع %	العدد	نسبة غير الرئوي من المجموع الكلي %		
2010	186	117	63	150	45	336	5.5
2000	158	89	56	145	48	303	6.0
2001	178	94	53	157	47	335	6.5
2002	175	91	52	128	42	303	5.7
2003	169	108	64	139	45	308	5.6
2004	146	91	62	176	55	322	0.6
2005	162	86	53	187	54	349	6.4
2006	174	104	60	181	51	355	6.3
2007	179	109	61	154	46	333	5.8
2008	172	104	60	165	49	337	5.8
2009	173	109	63	190	52	363	6.1
2015	0	0	0	0	0	0	0.0
2011	184	103	56	128	41	312	5.0
2012	158	85	54	172	52	330	5.2
2013	182	85	47	142	44	324	5.0
2014	218	117	54	161	42	379	5.7
2016	317	85	27	143	31	460	4.7

PATHOGENESIS

Infection by M. tuberculosis proceeds in steps, from initial infection of macrophages to a subsequent TH1 response that both contains the bacteria and causes tissue damage. These steps are:

1. **Entry into macrophages**. M. tuberculosis enters macrophages by phagocytosis mediated by several receptors expressed on the phagocyte, including mannose binding lectin.

2. **Replication in macrophages**. M. tuberculosis inhibits maturation of the phagosome and blocks formation of the phagolysosome, allowing the bacilli to replicate unchecked within the phagosome, protected from the microbicidal mechanisms of lysosomes.

The bacterium blocks phagolysosome formation by inhibiting Ca2+ signals and the recruitment and assembly of the proteins that mediate phagosome-lysosome fusion. Thus, during the earliest stage of primary tuberculosis (<3 weeks) in the nonsensitized individual, bacteria proliferate in the pulmonary

alveolar macrophages and air spaces, resulting in bacteremia and seeding of multiple sites. Despite the bacteremia, most people at this stage are asymptomatic or have a mild flu-like illness.

3. Multiple pathogen associated molecular patterns of M. tuberculosis, including lipoproteins and glycolipids, are **recognized by innate immune receptors (by the pattern recognition receptors**) , including Toll-like receptors. This initiates and enhances the innate and adaptive immune responses to M. tuberculosis

4**. The TH1 response**. *About 3 weeks* after infection, **a T-helper 1 (TH1) response is mounted** that activates macrophages, enabling them to become bactericidal. The response is initiated by mycobacterial antigens that enter draining lymph nodes and are displayed to T cells.

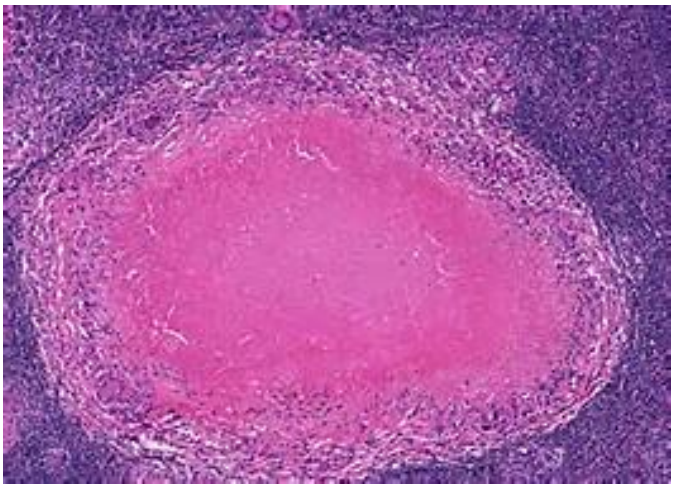
Differentiation of TH1 cells depends on IL-12, which is produced by antigen-presenting cells that have encountered the mycobacteria. Stimulation of toll like receptors by mycobacterial ligands promotes production of IL-12 by dendritic cells.

5. **TH1-mediated macrophage activation and killing of bacteria**. TH1 cells, both in lymph nodes and in the lung, produce IFN-γ. IFN-γ is the critical mediator that enables macrophages to contain the M. tuberculosis infection.

6. **Granulomatous inflammation and tissue damage**. In addition to stimulating macrophages to kill mycobacteria, the TH1 response orchestrates the formation of granulomas and caseous necrosis. Macrophages activated by IFN-γ differentiate into the “epithelioid histiocytes” that aggregate to form granulomas; some epithelioid cells may fuse to form giant cells.

In many people this response halts the infection before significant tissue destruction or illness occur. In other people the infection progresses due to advanced age or immunosuppression, and the ongoing immune response results in caseation necrosis.

Caseating granuloma



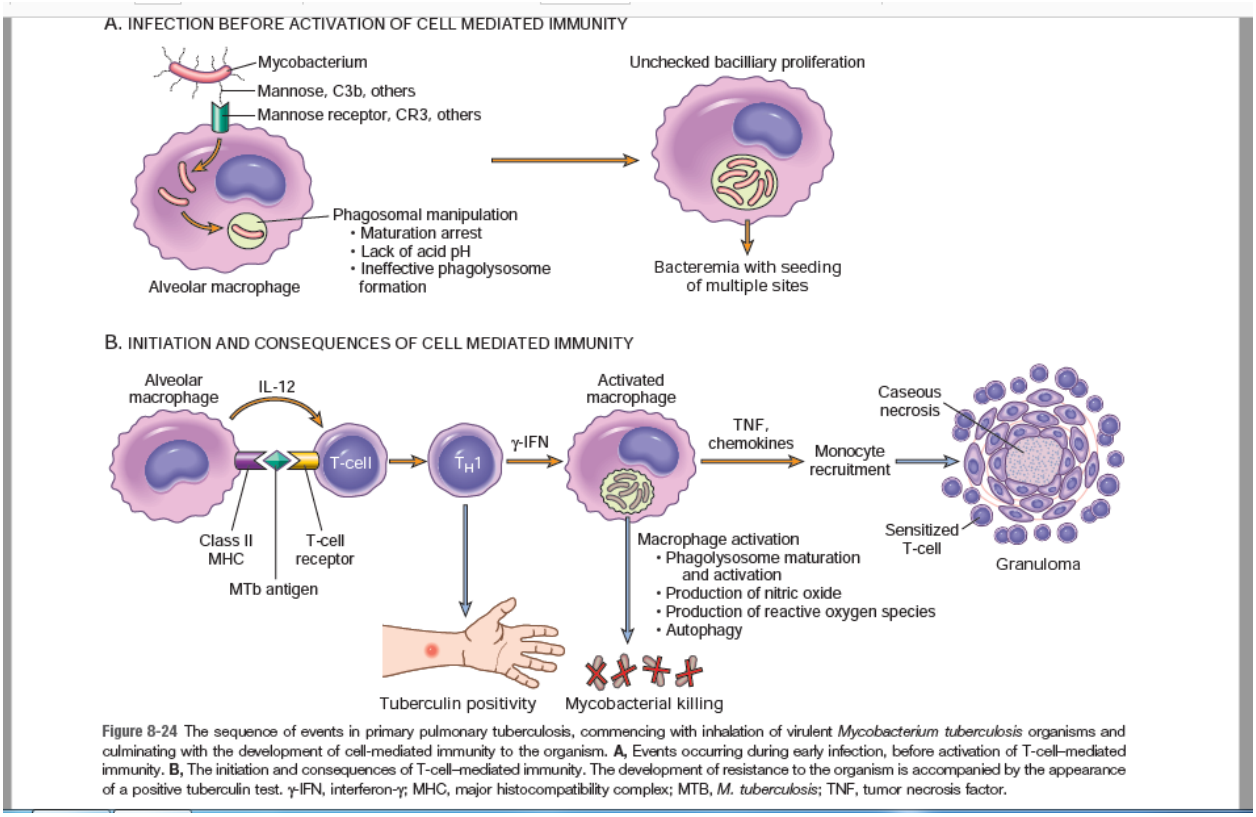
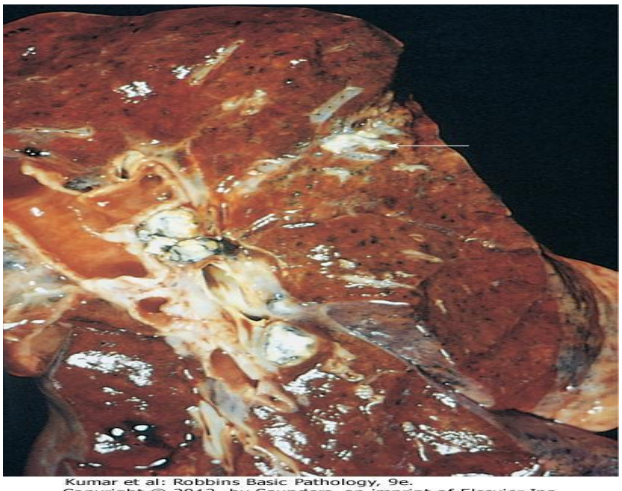


Figure 8-24 The sequence of events in primary pulmonary tuberculosis, commencing with inhalation of virulent *Mycobacterium tuberculosis* organisms and culminating with the development of cell-mediated immunity to the organism. **A,** Events occurring during early infection, before activation of T-cell–mediated immunity. **B,** The initiation and consequences of T-cell–mediated immunity. The development of resistance to the organism is accompanied by the appearance of a positive tuberculin test. γ-IFN, interferon-γ; MHC, major histocompatibility complex; MTB, *M. tuberculosis*; TNF, tumor necrosis factor.

Clinical presentation:

Primary TB: Is the form of disease that develops in previously unexposed and unsensitized patient. It presents as granulomas in the primary lung site, these are called Ghon focus . Ghon focus with associated granulomas in the draining lymph nodes are called Ghon complexes

Gohn complex:



The Ghon complex undergoes progressive *fibrosis*, followed by radiologically detectable calcification which is called **Ranke complex**

These 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. But uncommonly, they may lead to **progressive primary tuberculosis** and this complication occurs in immunocompromised patients.

Secondary TB: Is the pattern of disease that arises in a previously sensitized host.

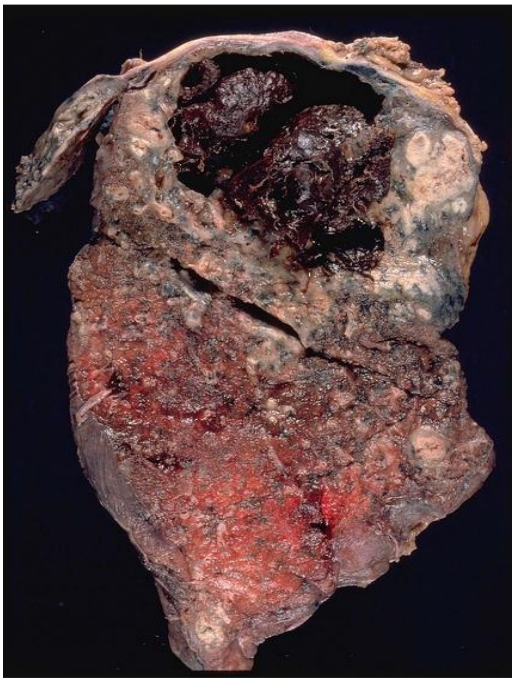
a. It may follow shortly after primary tuberculosis,

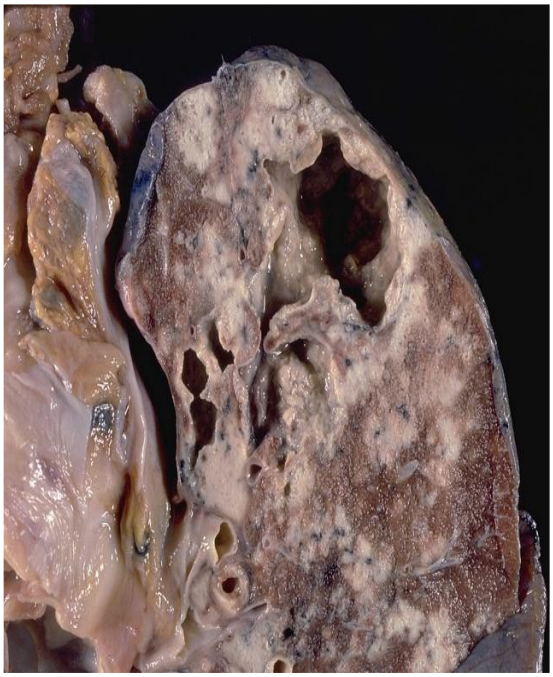
b. More commonly arises from reactivation of dormant primary TB decades after initial infection, particularly when host resistance is weakened.

NOTE: 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 marked tissue response to wall off the focus. Cavitation (pic below) occurs in secondary TB due to tissue loss.

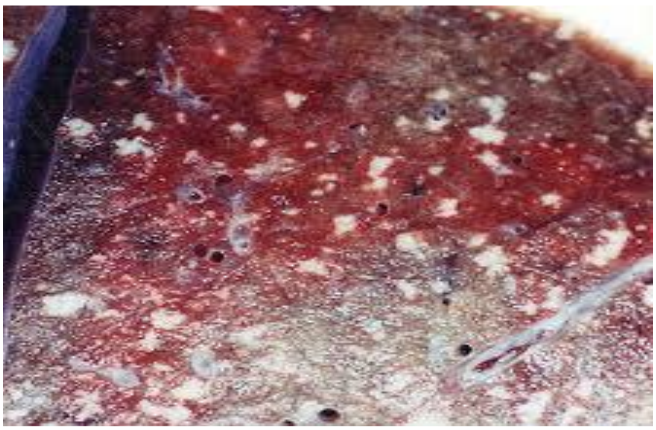




Miliary TB: means spread of TB through blood

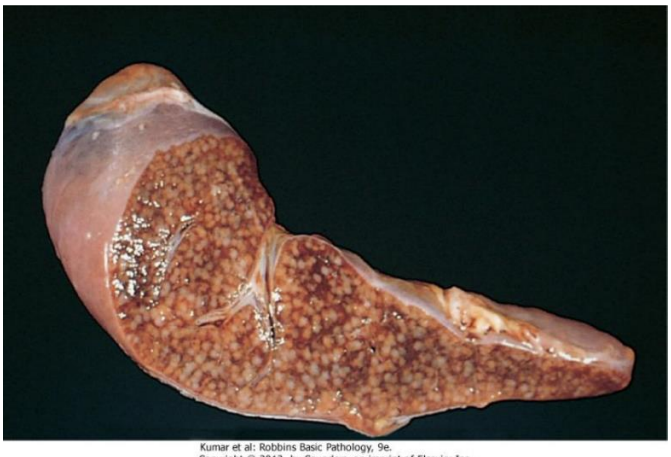
1. Miliary pulmonary disease (pic below) . Occurs when organisms drain through lymphatics into the lymphatic ducts, then empty into the venous return to the heart and then into the pulmonary arteries

-Individual lesions are small, (2 mm) foci scattered through the lung parenchyma



2. Systemic miliary tuberculosis

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



3. Isolated-organ tuberculosis

-Tuberculous involvement of Vertebrae is called (Pott disease).