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Tuberculosis Pathophysiology and Diagnosis: A Review Article

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Abstract

Tuberculosis (TB) is an infectious disease caused by bacteria from the *Mycobacterium tuberculosis* group. According to the 2015 WHO report, at the global level it was estimated that 9.6 million new TB cases were present. With 1.5 million deaths due to TB of which 480,000 cases are women. Several risk factors that increase a person to become sick with TB are the concentration of inhaled germs, length of time since infection, age, level of immune system (HIV/AIDS, malnutrition, immunocompromise). If massive spread through the bloodstream can cause miliary TB. Aim of this study is to review TB Diagnosis and Pathophysiology. Tuberculosis germs that enter through the respiratory tract will lodge in the lung tissue, where it will form a pneumonic nest, which is called the primary nest or primary affect. These primary nests may arise anywhere in the lung, in contrast to reactivation nests. From the primary nest will be seen inflammation of the lymph channels to the hilus (local lymphangitis). The inflammation is followed by enlargement of the hilar lymph nodes (regional lymphadenitis). The primary affect together with regional lymphangitis is known as the primary complex. From this primary tuberculosis will appear many years later post-primary tuberculosis, usually at the age of 15-40 years. Post-primary tuberculosis has various names, namely adult form of tuberculosis, localized tuberculosis, chronic tuberculosis, and so on. This form of tuberculosis is primarily a public health problem, because it can be a source of transmission. Post-primary tuberculosis begins with early hives, which are generally located in the apical segment of the superior and inferior lobes. This early nest initially takes the form of a small pneumonic nest The diagnosis of TB can be established based on the results of bacteriological or clinical examination. The diagnosis of TB must be pursued bacteriologically with the discovery of Mycobacterium tuberculosis. In miliary or disseminated TB, each organ can be named according to the severity of infection.

Keywords: Tuberculosis, Diagnosis, Pathophysiology, Mycobacterium tuberculosis, Tuberculin test.

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Introduction

Tuberculosis is an infectious disease caused by bacteria from the *Mycobacterium tuberculosis* group. Mycobacterium species consist of *M. Tuberculosis*, *M. Africanum*, *M. Bovis*, *M. Leprae*, and so on. This group is also known as acid-fast bacteria (BTA). Mycobacterium germs that cause respiratory tract disorders, in addition to *Mycobacterium tuberculosis*, are referred to as MOTT (Mycobacterium Other Than Tuberculosis) [1].

The characteristics of *Mycobacterium tuberculosis* as Rod shape, 1-10 micron long, 0.2-0.6 micron, wide. Need special culture media: Lowenstein Jensen, Ogawa. Under a microscope it looks like a red rod-shaped bacterium. Low temperature resistance, can last a long time at temperatures between 4°C to minus 7°C. Very sensitive to heat, sunlight and ultraviolet light. Germs will die by exposure to ultraviolet light within a few minutes. In phlegm at temperatures between 30°C-37°C will die in approximately 1 week but can be dormant [2].

According to the 2015 WHO report, at the global level it was estimated that 9.6 million new TB cases were present. With 1.5 million deaths due to TB of which 480,000 cases are women. Of the TB cases, 1.1 million (12%) were found to be HIV positive with 320,000 deaths and 480,000 Drug Resistant TB (TB-RO) with 190,000 deaths. Of the 9.6 million new TB cases, it is estimated that 1 million TB cases in children (under 15 years of age) and 140,000 deaths/year [3].

Several risk factors that increase a person to become sick with TB are the concentration of inhaled germs, length of time since infection, age, level of immune system (HIV/AIDS, malnutrition, immunocompromise). About 10% of those infected with TB become ill with TB, but the risk increases for being HIV positive. TB generally occurs in the lungs but spread through the bloodstream or lymph can cause TB outside the lungs (Extrapulmonary TB). If massive spread through the bloodstream can cause miliary TB [4]. Aim of this study is to review TB Diagnosis and Pathophysiology.

The mode of transmission of Tuberculosis (TB) is through inhalation of air containing sputum droplets of smear positive TB patients (65%), negative smear TB with positive culture results (26%), while TB patients with negative culture results and positive chest X-ray (17%). One cough can produce about 3000 sputum sprinkling. Which contains germs as much as 0-3500 M. tuberculosis. Meanwhile, if you sneeze, you can release as much as 4500-1,000,000 M. tuberculosis [1, 2].

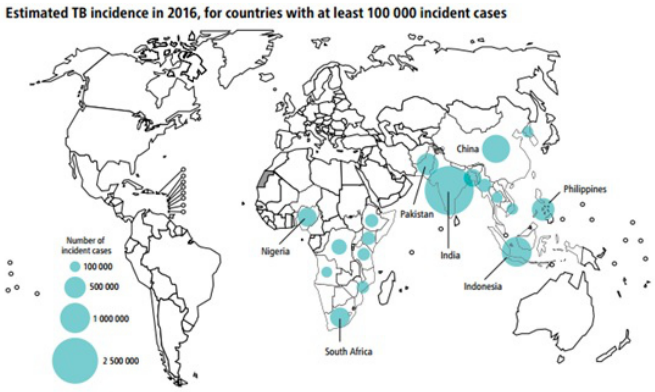

Figure 1. Estimated TB Incidence Worldwide [4]

Pathophysiology of Tuberculosis

The pathogenesis of TB when viewed from the infection process, could be primary and post-primary tuberculosis [5, 6].

Primary Tuberculosis

Tuberculosis germs that enter through the respiratory tract will lodge in the lung tissue, where it will form a pneumonic nest, which is called the primary nest or primary affect. These primary nests may arise anywhere in the lung, in contrast to reactivation nests. From the primary nest will be seen inflammation of the lymph channels to the hilus (local lymphangitis). The inflammation is followed by enlargement of the hilar lymph nodes (regional lymphadenitis). The primary affect together with regional lymphangitis is known as the primary complex [5].

This primary complex will suffer one of the following fates. Heal without leaving any defects at all (restitution ad integrum). Healed by leaving a few scars (eg Ghon's nest, fibrotic lines, calcareous nests at the hilum) [7]. Then spread by:

a. Continuitatum, spreading around. One example is epituberculosis, which is an event in which there is

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compression of the bronchi, usually the middle lobe bronchus, by the enlarged hilar glands, causing obstruction of the airways concerned, resulting in atelectasis. Tuberculosis germs will spread along the blocked bronchi to the atelectasis lobe and cause inflammation in the atelectasis lobe, known as epituberculosis [3, 5].

b. Bronchogen spread, both in the lung concerned and to the lung next to it. This spread also occurs into the intestine [7].

c. Hematogenous and lymphogenous spread. The incidence of this spread is closely related to the immune system, the number and virulence of the bacilli. The resulting nest can heal spontaneously, but if there is no adequate immunity, this spread will cause serious conditions such as miliary tuberculosis, tuberculous meningitis, typhobacillosis Landouzy. This spread can also cause tuberculosis in other body organs, such as bones, kidneys, children's kidneys, genitalia and so on. This complication and spread may end in recovers with sequelae [7] (eg growth retardation in children after encephalomeningitis, tuberculoma).

Post-Primary Tuberculosis

From this primary tuberculosis will appear many years later post-primary tuberculosis, usually at the age of 15-40 years. Post-primary tuberculosis has various names, namely adult form of tuberculosis, localized tuberculosis, chronic tuberculosis, and so on. This form of tuberculosis is primarily a public health problem, because it can be a source of transmission. Post-primary tuberculosis begins with early hives, which are generally located in the apical segment of the superior and inferior lobes. This early nest initially takes the form of a small pneumonic nest [8].

The fate of this pneumonic nest will follow one of the following paths:

1. Re-absorbed, and recovered with no defects [1].

2. The nest was initially expanded, but soon the healing process occurred with fibrotic tissue effusion. Furthermore, it will wrap itself to become harder, calcification occurs, and will heal in the form of calcification. On the other hand, the nest can become active again, forming cheese tissue and causing cavitation when the cheese tissue is coughed out [7].

3. The pneumonic nest expands, forming a network of cheese (caseous tissue). The caviti will appear by coughing the cheese tissue out. Cavities initially thin-walled, then the walls will become thick (sclerotic cavities). The fate of this cavity [9]-

May expand again and give rise to new pneumonia nests. This pneumonic nest will follow the pattern of travel as mentioned above.

Can also condense and wrap themselves (encapsulated), and is called a tuberculoma. Tuberculomas can calcify and heal, but they may also reactivate, thaw again and become cavitary again

Cavity can also be clean and heal which is called an open healed cavity, or cavity heals by wrapping itself up, eventually shrinking. It may end up as an encased cavity, and shrink to a stellate shaped appearance.

Classification of TB based on the anatomical location of the disease consists of pulmonary and extra pulmonary tuberculosis. TB located in the lung parenchyma. Miliary TB is considered as pulmonary TB because of the presence of lesions in the lung tissue. Patients who suffer from pulmonary TB as well as extrapulmonary TB are classified as pulmonary TB. TB that occurs in organs other than the lungs, such as the pleura, lymph nodes, abdomen, urinary tract, skin, joints, lining of the brain and bones. TB lymphadenitis in the chest cavity (hilar and/or mediastinal) or pleural effusion without radiological findings suggestive of pulmonary TB, extrapulmonary TB is defined [1, 6].

Signs and symptoms in patients with tuberculosis (TB) include, first, coughing up phlegm for 2 weeks or more. Sputum mixed with blood, coughing up blood and shortness of breath. Furthermore, the body is weak, appetite decreases and weight decreases. Usually night sweats without physical activity and fever for more than 1 month [9].

In HIV-positive patients, TB symptoms are often non-specific and the cough does not have to last for 2 weeks or more. Fulminant hepatitis can show symptoms of jaundice, seizures, and even unconsciousness. such as close contact with TB patients, living in densely populated areas, slum areas, refugee areas, and others [1, 3].

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Additional symptoms in extrapulmonary TB patients, symptoms and complaints depend on the organ affected, for example neck stiffness in TB meningitis, chest pain in TB pleura (pleurisy), enlarged superficial lymph nodes in TB lymphadenitis, spinal deformity (gibus) in TB spondylitis, and etc [5].

Diagnosis of Tuberculosis

The diagnosis of tuberculosis (TB) is determined based on complaints, the results of the history, clinical examination, laboratory examinations and other supporting examinations.

Tests that can be done in patients with suspected TB [10]:

a. Bacteriological examination

1. Direct microscopic examination of sputum

The purpose of sputum examination is to establish a diagnosis, determine the potential for transmission, and assess the success of treatment. Sputum examination collects

2 samples of the morning sputum test (SP) [11]:

• S (When): phlegm is collected at the health service

• P (Morning): Sputum is collected in the morning immediately after waking up, it can be done at the patient's home or in the inpatient ward.

2. TB Molecular Rapid Test (TCM) Examination

The method used is Xpert MTB/Rif. TCM is a tool for diagnosis, but is not used to evaluate treatment outcomes.

3. Culture Check

Culture examination with Lowenstein-Jensen solid media and liquid media (Mycobacteria Growth Indicator Tube). This examination is intended to establish a definite diagnosis of TB in certain patients, such as extra-pulmonary TB, paediatric TB, and TB with negative direct smear microscopic sputum examination results [12].

b. Other supporting examinations

1. X-ray examination

2. Histopathological examination in suspected cases of extrapulmonary TB

c. Drug sensitivity test

Drug sensitivity test to determine the presence or absence of *Mycobacterium tuberculosis* resistance to anti-tuberculosis drugs (OAT) [12].

d. Serological examination

In Indonesia, until now it has not been recommended for serological examination in addition to the general examination, several tests that can be used to detect *M. tuberculosis*, namely TST and IGRA, also need to be performed on people who are at high risk of exposure to TB and live in TB endemic areas. Specially to find out latent TB infection. The tests carried out are:

1. Mantoux tuberculin skin test (TST) [13]

Tuberculin assay is used to measure cellular immunity of delayed type hypersensitivity (DTH) to purified protein derivative (PPD) tuberculin, which is an antigen for various mycobacteria including *M. tuberculosis*, BCG *M. tuberculosis*, BCG *M. bovis* and various mycobacteria in the environment. How to read TST [14]:

• Tuberculin test results are read 48-72 hours after the injection is done

• Measure the induration, not the redness

• Measurements are written in millimetres

• Interpretation of results:

o 5 mm positive if: HIV patients, close exposure to TB, patients with positive but untreated chest X-ray, organ transplant recipients, and other immunocompromised persons (prednisone >15 mg/day for 1 month or receiving TNF- antagonists).

o 10 mm positive induration in: immigrants from endemic areas, injection drug users, hospital residents or employees, members of the microbiology laboratory, conditions at high risk of TB, people exposed to TB patients at high risk of transmission [8, 9].

o 15 mm positive induration in patients without TB risk factors.

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o False positive for: non-tuberculosis Mycobacterium infection, and BCG vaccine recipients.

o False negative in: anergy (decreased immune response to TST), infants <6 months, newly infected with TB <10 weeks, new live virus vaccines (measles and smallpox) decreased TST reactivity, wrong way of TST injection (too deep or too low) a little) [8, 14].

2. Interferon-gamma release assays (IGRA)

The IGRA test uses a blood sample, by assessing interferon gamma released by blood cells in response to antigens. The types of IGRAs available in the United States and approved by the Food and Drug Administration (FDA) are the QuantiFERON-TB-Gold-in-tube test (QFT-GIT) and the T-SPOT TB test (T-Spot). IGRA assesses familial interferon gamma in blood samples for the presence of antigen, then the results are compared with controls. IGRA results can be obtained within 24 hours. A history of BCG vaccine will not lead to a false positive result. However, the use of IGRA is limited and cannot be used in children <5 years, people newly infected with M. tuberculosis, and immunocompromised people, because it is expensive, and cannot be used as a serial test [15-17].

Conclusion

The diagnosis of TB can be established based on the results of bacteriological or clinical examination. The diagnosis of TB must be pursued bacteriologically with the discovery of Mycobacterium tuberculosis. If the TB process is present in several organs, the name is according to the organ affected by the heaviest TB process.

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