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CLINICAL ASPECTS OF TUBERCULOSIS DISEASE

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Annotation*: This article provides a general understanding of tuberculosis, causative mycobacteria and their types, transmission routes, clinical aspects of the disease, diagnosis, treatment and prevention.*

Keywords: *tuberculosis, mycobacterium tuberculosis, mycobacterium bovis, HIV, BACTECMGIT-960.*

Pulmonary tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Other mycobacteria can also produce pulmonary tuberculosis and these include *M. tuberculosis, M. africanum, M. microti, M. canetti, M. pinnipedii, M. caprae,M. bovis, M. bovis*. Usually, patients with pulmonary tuberculosis who have cavitary lesions are an important source of infection. These patients are sputum smear-positive. Coughing produces tiny infectious droplets. Usually, one bout of cough produces 3000 droplet nuclei and these can stay in the air for a long period of time. Ventilation removes these infectious nuclei. *Mycobacterium tuberculosis* can survive in the dark for several hours. Direct exposure to sun light quickly kills these bacilli. Of the various factors, determining an individual's risk of exposure, two factors are important. These include the concentration of droplet nuclei in contaminated air and the length of time that air is breathed. The risk of transmission of infection from a person with sputum, smear-negative pulmonary tuberculosis and miliary tuberculosis is low and with extrapulmonary tuberculosis infection is even lower. However, infection with *Mycobacterium bovis*occurs through milk. Human infection from *Mycobacterium bovis* is rare in Uzbekistan because milk is often boiled before use. Even though non-tuberculosis mycobacteria are harmless, some can cause human disease especially in immunocompromised individuals.

The cardinal event in the pathogenesis of tuberculosis, whether inapparent or overt is the implantation of *Mycobacterium tuberculosis* in the tissues. Lung is the most frequent portal of entry. The organism enters the lung from the inhalation of air borne droplets which have been coughed out by 'open' [sputum-positive] pulmonary tuberculosis patients who have received no treatment, or have not been treated fully. Droplet nuclei are airborne particles of water, usually 1 to 4 micrometers in diameter, in which the bacilli travels. Deposition of bacilli occurs in the alveoli by sedimentation. Gravitational forces in the peripheral lung regions where airflow velocity is low aid in the sedimentation of bacilli. This elicits a local inflammatory response with neutrophils and resident macrophages during the first 48 hours. The organisms proliferate in the alveoli at the periphery of the lung, often beneath the pleura forming a Ghon's focus. Acute inflammatory response that occurs at the site of implantation may result in some cell death. As im m une response has not developed, the organism is not destroyed and they are conveyed to regional lymph nodes at hilum resulting in proliferation of bacteria in the lymph nodes. Immune response develops 4 to 6 weeks after inhalation and activated T cells recruit monocytes and mononuclear cells to the lung and lymph nodes, ultimately leading to granulomatous inflammation with giant cells, epitheloid cells and lymphocytes and caseation. Usually the Ghon's focus and caseating granuloma in lymph nodes heal by collagen deposition around the

tubercle. The lesion at the primary site of involvement, draining lymphatics and the inflammed regional lymph nodes constitute the primary complex. When the primary site of implantation is in the lung, it is called Ghon's focus. The draining lymphatics and the involved lymph nodes together with Ghon's focus constitute the primary complex [Ghon complex]. In children, the lymph node component may be much larger than the Ghon's focus. Viable bacteria may remain walled offwithin the healed primary complex leading to latent tuberculosis. Progressive primary tuberculosis results in individuals who are unable to mount an appropriate immune response. Spread of infection can occur when lymph nodes erode through the wall of a bronchus or a blood vessel. Ghon focus, though small, can rupture through the visceral pleura to produce tuberculous pleurisy. In 75% cases, it occurs within 5 months of infection. Bronchial spread of the organisms may result in extensive confluent granulomatous lesions and this may be fatal. Spread of the organisms through blood stream results in miliary tuberculosis. If the lymph nodes erode into a pulmonary vein, this results in systemic dissemination of the organisms. If node ruptures into a pulmonary artery, miliary dissemination tothe lungs occur. Less commonly, tubercle bacilli may be ingested and lodge in the tonsil or in the wall of the intestine. This form of tuberculosis occurs following the ingestion of contaminated milk or milk products. Rarely, tuberculosis can occur as a result of direct implantation of the organisms into the skin through cuts and abrasions. This form of tuberculosis is a health hazard faced by health care workers and laboratory staff who handle materials infected with *Mycobacterium tuberculosis*. These lesions were termed "prosector's warts". Interestingly, Laennec, the inventor of the stethoscope, acquired tuberculosis in this fashion which eventually led to his death.

Thus, primary tuberculosis is a widely disseminated infection. This fact is not realized by clinicians. Most of the metastatic foci heal. However, some of these metastatic foci may remain dormant and may reactivate at a later date when the host resistance decreases. The subsequent course of the events varies considerably. In most of the patients, the primary complex resolves without becoming clinically apparent. This occurs when the immune status of the host is good, and healing occurs by fibrosis and calcification. In a minority of patients, progressive primary tuberculosis due to the extension of the inflammatory process at the site of the primary focus can occur. In the lung, this can present as an area of consolidation [tuberculosis pneumonia]. This form of the disease was often encountered in the prechemotherapeutic era and was termed "galloping consumption" or "pneumonia Alba" [white pneumonia]. This form is encountered in the present era in patients with. Human immunodeficiency virus (HIV) infection: Caseation necrosis at the Ghon's focus may lead to liquefaction. Expectoration of the liquefied material can leave a cavity with shaggy margins in the pulmonary parenchyma which may be apparent on the chest radiograph.

Tuberculosis infection refers to a positive tuberculin test without evidence of active disease. Tuberculosis disease refers to active disease with positive acid fast smear or culture for *M. tuberculosis* or radiographic and clinical presentations of tuberculosis.

Diagnostic tools that are available today for the rapid diagnosis of tuberculosis have remained largely the same since the discovery of tubercle bacillus by Robert Koch more than a century ago. The main diagnostic tools are:

Clinical characteristics,

Tuberculin skin testing,

Chest radiography,

Sputum smear microscopy,

Culture of bacteria,

Serology and antigen detection and

Molecular diagnostic methods

Clinical Characteristics

A high clinical index of suspicion is the most important factor in the early diagnosis of tubercul0sis especially in primary tuberculosis. Clinicians should be aware of the groups in which tuberculosis is more common. These include patients with HIV infection, the elderly, persons born or residing in places where infection with tuberculosis is common, close contacts of known cases of active tuberculosis, persons with malignancy, malnutrition, or diabetes mellitus, and persons receiving immunosuppressive therapy or underlying lung diseases such as silicosis.

In vast majority of cases, primary infection is asymptomatic or minimally symptomatic with fever, dry or scant sputum production. Occasionally patient may develop retrosternal pain or erythema nodosum. Primary infection can cause clinical pneumonia in 5 to 10% adults. This percentage may be higher in children and HIV infected persons. In older infants and children, primary pulmonarytuberculosis usually produces no signs or symptoms and a chest X-ray shows no signs of infection. Rarely, there may be enlargement of lymph nodes, and perhaps some coughing. In most cases tuberculin skin test is positive. This primary, infection usually resolves on its own as the child develops immunity over a six to ten week period. But in some cases, it can progress and spread all over the lungs (progressive tuberculosis) or to other organs. This causes systemic signs and symptoms such as fever, weight loss, fatigue and loss of appetite, and signs and symptom referable to the organ involved. It has been estimated that approximately 10% of individuals with normal immunity will develop active TB within their life time, and 5% within the first two years of infection. The progression from TB infection to disease is related to host factors such as genetics, nutritional status and immune competence. The incidence of TB in HIV-infected persons is more than 100 times that of general population. The risk of TB developing in an HIVinfected person who is latently co-infected with *Mycobacterium tuberculosis* is approximately 12% per year

Tuberculosis should be suspected in patients presenting with the following symptoms and history:

Adults:

1. Cough more than three weeks,
2. Blood in the sputum,
3. Chest pain for more than one month.
4. Increasing weakness and loss of weight and
5. Had tuberculosis in the past or previously treated for cough?

However, the clinical characteristics are non-specificand these symptoms point to do further

Tuberculin Skin Testing:

Even though a positive response to tuberculin which has been described more than 100 years ago is not diagnostic of tuberculosis, it significantly increases the suspicion of tuberculosis. It is a simple, cheap and easy to read test. Tuberculin test is performed using PPD-S or PPD-RT23. The

strength of PPD is expressed in terms of International Units (IU). One unit of PPD-RT 23 corresponds to about three IU of PPD-S. For diagnostic purpose, the test is performed with 5 IU PPD-S or one or two units of PPD-RT 23+ Tween 80. Tween 80 is used as a detergent to prevent the tuberculin sticking to the glass. Tuberculin test is performed by injecting one unit of PPD-RT 23+ Tween 80 intradermally producing a lump in the skin of 5-6 mm diameter. The skin test reaction is read 48 to 72 hours later. If positive, an area of erythema and an area of induration of the skin is seen. The diameter of the induration is measured across the transverse axis of the arm. A positive reaction ts a diameter of 10 mm or more with one PPD-RT23 In subjects who has not been vaccinated with BCG. If a child is vaccinated with BCG, a diameter of over 15 mm is recognized as positive, suggesting that this child has also been infected with *M.tuberculosis*. A positive result means that the person is infected by *M. tuberculosis*, but it does not mean that he/she has tuberculosis disease. Similarly, a negative test means that the person has not been infected with M. tuberculosis. However, It does not exclude infections with *M. tuberculosis*. A number of factors can suppress tuberculin reactions e.g. malnutrition, HIV infection, measles, chicken pox, cancer, severe bacterial infections (including tuberculosis) and corticosteroids. It may also be negative, if tuberculin test is performed in a person soon after inhaling the organtsm. It does not differentiate primary and secondary infections, and active and inactive diseases.

Chest Radiography

Chest radiography is widely used for detecting cases of pulmonary tuberculosis. However, no radiographic picture is typical of tuberculosis, and many lung diseases can have similar radiographic appearances mimicking pulmonary tuberculosis. It cannot distinguish active pulmonary tuberculosis from inactive and previously treated tuberculosis. Inaddition, chest radiography may not detect early stages of tuberculosis disease. Because many a time chest radiography is used as a means for the diagnosis of pulmonary tuberculosis by many physicians, it can lead to over-diagnosis of TB and unnecessary drug treatment. It has also been observed that, even among expert readers, on an average there was 25% of under-reading and about 2% of over-reading. It was also found that there was an intra-individual inconsistency of 20%, i.e. each reader changed his/her mind in about one-fifth of the cases he/she had classified as "positive" at the first reading. Even though chest radiography is not a reliable test for the diagnosis of pulmonary tuberculosis, it can be a useful supportive tool in the diagnosis of primary and smear negative pulmonary tuberculosis.

In primary tuberculosis, a lobar or segmental infiltrate characterized by ipsilateralhilaradenopathy is seen in chest radiographs. Hilaradenopathy may lead to compression of the bronchus and displacement of the great vessels and trachea. Resolution of primary tuberculosis may lead to a parenchymal nodule or Ghon's focus which becomes calcified with time. When a Ghon's focus is associated with calcified hilar lymph nodes, it is termed as primary or Ranke's complex. Primary tuberculosis infection may progress in a small percentage of patients resulting in pleurisy and pleural effusion, progressive caseous pneumonia, extensive broncho-pneumonia or hematogenous spread that leads to disseminated disease.

Computed Tomography (CT) is more sensitive than chest radiography for detection of lymphadenopathy, miliary disease, bronchiectasis, bronchial stenosis. broncho-pleural fistula and pleural effusions. CT may reveal occult abscesses and the extent of pleural disease. Magnetic resonance imaging is useful in extrapulmonary disease, such as skeletal and intracranial tuberculosis.

Sputum Smear Microscopy

Detection of acid fast bacilli in clinical specimens described by Robert Koch more than a century ago is still the most important diagnostic test in tuberculosis. It is cheaper, easier and more reliable than chest radiographs and tuberculin testing, and cheaper and easier than culturing of *Mycobacterium tuberculosis*. Even though acid fast bacilli (AFB) stain of sputum is positive in up to 75% of adults with pulmonary TB, fewer than 20% of children with TBhave a positive AFB smear of sputum or gastric aspirate. Fluorochrome stains such as auramine and rhodamine are superior to classical carbolfuchsin stains. The lower limit of detection of AFB sputum smear is of 0.5 - lx 104 micro-organisms mL -1 of sample. AFB smears cannot distinguish *M.tuberculosis* from other mycobacteria. It also cannot distinguish dead organisms from live ones.

Culture of Mycobacteria

Isolation of *M. tuberculosis* in culture from clinical specimens is the gold standard for the diagnosis of tuberculosis. Culturing is more sensitive than sputum smear microscopy. But it is an expensive method requiring trained personal. It takes 7-8 weeks to obtain culture results in conventional solid media and this delays confirmation of the diagnosis and starting treatment. Culturing is therefore inappropriate as a diagnostic tool, but can be used to test drug susceptibility. Culturing is also useful in sputum smear-negative cases where active TB is suspected. There should be a minimum of 100 mycobacteria per ml for a positive culture. In routine laboratories, a large proportion of positive cultures are due to contamination. BACTEC MGIT-960 technique is a semi-automated radiometric liquid culture system to detect the growth of mycobacteria more quickly than is possible with conventional solid media. BACTEC MGIT-960cultures may become positive as soon as 1-2 weeks after inoculation. However, it is an expensive system. With the Septi-Check technique, the rate of recovery is higher than that with conventional cultures and with BACTECMGIT-960technique.

Currently.serological investigations have no value in the diagnosis of tuberculosis. The polymerase chain reaction (PCR) is a technique that allows the rapid detection and quantification of few DNA copies with very high sensitivity and specificity. Diagnostic PCR involves DNA amplification using DNA sequences as markers for microorganisms.

Treatment

Treatment of tuberculosis is by using appropriate regimens of six or eight month duration. Sputum smear-positive new pulmonary tuberculosis patients are treated with a six month regimen that includes the first two months of intensive phase With isoniazid(H], rifampicin[R], ethambutol[E] and pyrazinamide[Z] followed by the next four months with isoniazid and rifampicin. Patients with relapse and resistant form of tuberculosis can be treated with a eight month regimen that includes threemonths intensive phase with HREZ(during the first a two months of intensive phase, given) followed by next five months with HRE.

Sputum smear negative tuberculosis is treated witha six month regimen. Initial intensive phase of two months is with HRZ followed by the next four months with HR. In all regimens the drugs can be given either daily or three times a week.

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