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Overview of Tuberculosis Covering Pathogenesis, Clinical Manifestations, Diagnosis, Treatment Strategies, and Global Impact

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ABSTRACT

Tuberculosis appears to be one of the most common diseases around the world. Tuberculosis is mainly an airborne-sickness which is caused by the agent *Mycobacterium tuberculosis*. The disease is more prevalent in the third world countries with poor living conditions and highly endemic regions. The causative agent primarily affects the lungs leading to severe coughing and chest pains. The clinical features are usually presented with wide range of symptoms. Though the infection is more common in adults but the children are too prone to this life-threatening disease. According to the current investigations, this review provides an insight into the clinical manifestations, laboratory diagnosis and available treatment for tuberculosis.

Keywords: Alveolar Macrophages, Hemoptysis, Erythema Nodosum, Intrathoracic, Extrathoracic

Tuberculosis

Introduction

Considered as one of the most oldest and ancient diseases, tuberculosis has been simply evolved with the evolution of humans for several thousand years. Tuberculosis is an infectious bacterial disease which is caused by the bacterium: *Mycobacterium tuberculosis* (1).TB is primarily an airborne disease which spreads by the coughing or sneezing of an infected individual and results in presentations of lung infection, severe chest pains and coughing (2). TB is one of the most common and serious diseases prevalent globally. Infact after AIDS and Malaria, tuberculosis

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is the top 3rd infectious disease which causes the maximum number of mortalities each year with about a ten million people getting infected every year (3) (1).

Back in the 18th century, an advice of good food and enough sleep was given to the patients by physician. But with progression of time, the mystical disease was found to be caused by the bacterium: *Mycobacterium tuberculosis*. The discovery was made by the renowned German microbiologist Robert Koch. This phenominal finding evoked hope for the eradication of this serious infectious disease which was even more contagious than plague (3).

However, later on, a number of researches and drug discoveries were made in order to combat the disease; which actually the increasing rate of growth in the number of tuberculosis patients throughout the world in mid 20th century. But again after the AIDS pandemic, there was a rise in the number of cases of tuberculosis and the disease still remains on top today causing the most morbidity and mortality (3).

Transmission

There has been a long discussion and research as to how TB is transmitted and what mechanisms and risk factors are underlying by the much simplified cycle as depicted generally, which typically occurs as the steps written below:

(1) A source of tuberculosis that is an infected patient
(2) Releases the infectious particles as aerosols through coughing or sneezing
(3) These particles are able to survive for a period of time in the air
(4) The particles are then inhaled by the vulnerable individual
(5) Who may have the potential now to get infected with tuberculosis

The uncontrolled transmission of TB has added fuel to the already worsening situation. Though it is believed that tuberculosis occurs both outdoors and indoors but due an unlimited dilution outdoors and open areas it is less likely to contract the disease but on the contrary, indoor places specially those which are congested like houses with big families, prisons, refugee camps, factories and hospitals are the most vulnerable places because of a huge concentration and limited dilution (4).

TB is primarily an airborne disease which affects the alveolar macrophages. To get its reach into the lungs; a particle of about 1 to 5µm is required. As the droplet nuclei are the dehydrated residues of large particles which can accommodate more than one tubercle particles.

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Infact, dust released by shaking the bed sheets, clothes may also contain viable particles of *Mycobacterium Tuberculosis* but predominantly being attached to larger particles it only impacts the resistant upper respiratory tract rather than the lower one.

Duration and infectiousness of the TB for a person depends upon the various bacterial factors. It is believed that the infectiousness of TB is directly proportional to the smear positivity, thus patients are highly infectious who are presented with smear positive pulmonary tuberculosis. According to a study been conducted in family members of the house in Peru, smear positive cases were linked to a far greater risk of infection as compared to another study which showed the smear negative results. Nevertheless, smear negative TB can also be transmitted.

In short, droplet nuclei are generated by the patients who are suffering from laryngeal or pulmonary tuberculosis which are forced out through the airways by shouting, coughing, sneezing or any other expiration especially coughing being the most common factor in the generation of the infectious aerosols.

However, patients who have index TB and also infected with HIV with an advanced immunosuppressant are less likely to transmit the infection as compared to the non HIV, TB patients because of having a probability of smear negative tuberculosis and short duration of life (5).

Pathogenesis

In general, *M. tuberculosis* neither produces the exotins nor it contains any endotoxins in its cell wall. The bacterium primarily infects the macrophages and reticuloendothelial cells. The site of multiplication of *M. tuberculosis* is the cellular vacuole (the phagosome). The production of exported repetitive produced by the organism prevents the fusion of lysosome to the phagosome, thus preventing the degradation of the organism.

Events in the pathogenicity of *M.tuberculosis*

The first interaction of the organism as aerosol droplet occurs with the macrophages in the exposed human through the alveolar passageway. However there is also a possibility that the organism could also interact with the surface alveolar cells which are the pneumocytes (type 2). Though it is possible that organism is ingested by these cells rather than the macrophages as they are greater in number as compared

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to the macrophages. There are also other accessory cells which are called as the dendritic cells and play an important role as they are good presenters of the antigens, they are much better presenter of antigens as compared to the macrophages with playing a key role in the activation of the T cells with specific *M.tuberculosis* antigens (6)(7)(8).

The bacteria are further engulfed/ phagocytosed by the macrophages through their interaction with the cellular receptors which are mannose receptors on the surface and they are also termed as the complement receptors. The activity of receptors is further enhanced and regulated by the specialized proteins of the innate immune system called the surfactant protein A which is a water soluble protein and opsonizes the bacteria. On the contrary, the surfactant protein D is considered to inhibit the process by preventing the interaction of bacteria with the macrophage surface receptors. The trafficking of bacteria in the macrophages has also been shown to cause an inhibition in the Ca^{+2}signaling (6) (9).

Research has reported a lot of data on the entry and congregation of bacteria inside the host cells but not much is known about the later stages of bacterial survival and growth inside the lungs. It has been observed that the infected macrophages attract the inactivated neutrophils, lymphocytes, monocytes through the production of chemokines but it does not prove to be efficient enough in killing the bacteria(6). The healing of tubercle occurs through calcification and fibrosis.

This process controls and inhibits the spreading of bacteria and as there is enhancement of cellular immunity, the macrophages occupied by the bacteria are killed and a region of caseous center of granuloma is formed. It is considered that the bacteria do not multiply in this caseous tissue due to their inability of working efficiently in this unfavorable environment (acidic pH, toxic fatty acids) and a few organisms remain alive but they become dormant for decades. Now the infection is arrested permanently if the person is equipped with an efficient cell-mediated immunity (6).

Clinical Manifestations

The clinical features of tuberculosis are protean: generally covering a wide range of manifestations and involving many organs. Though, signs such as weight loss, fever, fatigue are also common.

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Pulmonary Tuberculosis: Pulmonary tuberculosis is basically the disease of the tracheobronchial region and the lung parenchyma (portion of the lungs which is involved in transferring the gases) only. However, the most classic and common features of the pulmonary TB include coughing, excessive night sweating, sudden loss in weight, loss of appetite, fatigue and **hemoptysis** which refers to the blood-stained mucus that is expelled out of mouth during coughing, it is also termed as the 'airway bleeding'. Though, hemoptysis is a common feature in lung cancer, and some other cardiovascular diseases. Patients with such clinical manifestations are mostly likely to suspected of having tuberculosis (10).

Primary Pulmonary Tuberculosis: The primary infection is usually presented as asymptomatic ailment but in some cases it causes infections of the lower respiratory tract. The regions with high TB prevalence, the primary infection is not usually common and might occur only childhood, though in countries with low tuberculosis prevalence, the primary infection may occur in adults as well. The primary infection is usually characterized by the granuloma (granulomatous inflammation) and is usually followed by the involvement of the lymph node which is called as the Ghon complex (lesion in the lung) (10).

The general complications of the disease include enlargement of the lymph node which mediates to bronchial obstruction, also pleurisy can also occur during the early phase of the infection. Some important disseminated forms such as **tuberculous osteomyelitis and tuberculous meningitis** constitute of the rare, serious complications. Though tuberculosis of the urogenital system may years later (10) (11).

Another characteristic of the primary infection is termed as the **erythema nodosum** which is basically the inflammation of the skin. More precisely the condition is presented as tender nodules along the extensor surfaces of the tibia and ulna and is a manifested in patients who are combatting the infection through a potent cell-mediated response (10).

Post Primary Pulmonary Tuberculosis: Post primary TB usually occurs years later after an individual has been vulnerable to the infectious TB and is accompanied by the immunological impairment. Though males are more susceptible to this

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manifestation as compared to females (10) (12). The generalized and most frequent signs and symptoms of this active disease include: night sweats, sudden weight loss, anorexia, anemia and severe coughing (persistent dry coughs) though there is also production of the blood stained sputum out of the mouth during the coughing. Moreover, cases are also presented with severe thoracic pain which is accompanied by the inflammation of the pleura (two thin layers which separate the lungs from the chest wall). Also in severe cases are presented with the severe erosion of the pulmonary blood vessels which ultimately results in hemoptysis (a condition which refers to the coughing up of the blood stained mucus); the patients are suffer from breathlessness (10).

Patients suffering from tracheobronchial or laryngeal tuberculosis may also present with hoarseness (breathy and strained voice) (10).

Extra Pulmonary Tuberculosis: This type of TB infection refers to the tuberculosis occurring at any site in the body other than the lungs. Though females are more susceptible and affected and a total of 10 to 40% of the adults are diagnosed with this type of tuberculosis. However many factors like ethnic background, age, the condition of the underlying disease, genotype of the strain are the key determinants of the severity of infection. As clearly it can affect any organ so a high index of clinical care is required. Accompanied by the typical symptoms of the infection, the patients often complain about the issues related to the affected organ. Nevertheless, the difference in area and origin has also largely affected the proportion and likelihood of acquiring the infection e.g. people in Asia are more vulnerable to acquire the intrapulmonary TB than those living in Germany (10) (13)(14).

Intrathoracic Lymph Node Tuberculosis: It is a type of extra pulmonary tuberculosis which is more common in children as compared to adults. The results are depicted by the chest radiography as the meditational enlargement which is accompanied by calcification. The enlarged lymph nodes could present bilaterally on the mediastinum or only one side of the mediastinum. Bronchial obstruction usually occurs as a result of too much enlargement of the lymph nodes such that their perforation into the bronchial tract may lead into the lobar pneumonia (10).

Extrathoracic Lymph Node Tuberculosis: It is one of the most frequent

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manifestations of the extra pulmonary tuberculosis. Around 30% of the people are presented with this type of extra pulmonary TB in Germany. Mostly cervical and supraclavicular lymph nodes are involved (14) (10).

Following the primary pulmonary tuberculosis, after 5 to 7 years, there are clinical manifestation of extra pulmonary TB which includes the bones and joints being affected. Especially skeletal TB comprises of around 8% of the cases in extra pulmonary infection and the probability is even higher in region with increased prevalence of the infection. Though rare but in some of the skeletal TB cases there is also involvement of the spine, a condition called as the Pott's disease (a rare infection of the spine, also known as the tuberculosis spondylitis and is considered to be a combination of both the osteomyelitis and arthritis). This typically initiates as the inflammation of the intervertebral disc mostly certainly involving the lower thoracic and the upper lumbar vertebrae, and usually presents in the first few weeks as a back pain accompanied with the abdominal pain. However there may be a palpation. In the late stage, kyphoscoliosis may develop which refers to an abnormal curve of the back. A collection of pus around the spinal cord develops which refers as the paraspinal abscess within the psoas muscle and results in pain in the groin (consisting of five muscles), in particular, on hip flexion (10).

Another most frequent and common manifestation of the extra pulmonary TB involves the genitourinary system which presents as the tuberculosis of the urinary bladder, kidneys and the female and male reproductive organs. It is the most common feature of the extra pulmonary disease and accounts for about 17% of such cases. Though systemic symptoms are less frequent and a variety of local symptoms occur depending on the organ involved. Though most of the cases are asymptomatic (15)(16)(17) (10).

Abdominal TB presents the involvement of ascites within the peritoneal cavity (collection of fluid inside the peritoneum; a covering around the abdominal organs) or any intra-abdominal organ. Though this type of tuberculosis is rare in the countries with low prevalence of the TB infection; in Germany it comprises of the 2% of EPTB cases. Ingestion of sputum or no pasteurized milk (*Mycobacterium bovis*) is considered to be the cause of the infection or by hematogenous spread. Although, TB occurs in any location of the gut from mouth to the anus, but it is more frequent

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in the ileum and caecum(18) (10).

This includes symptoms such as frequent abdominal pain and acute appendicitis. There is gastrointestinal bleeding and bowel obstruction. There may be involvement of the pancreas, liver and adrenal gland (10).

Tuberculosis of the central nervous system (CNS) includes tuberculous meningitis (TBM) which manifests slowly as the inflammation of the meninges. The most common local symptoms include the headaches. There are other symptoms ranging from seizures, vomiting, unconsciousness and symptoms attributable to the cranial nerves. Spinal meningitis (collection of the fluid around the spinal cord) is also a common feature of CNS tuberculosis with the involvement of peripheral nerves and there may be the presentation of paraplegia which includes the impairment of the sensory and motor nerves. Different factors associated with the scoring models have been utilized to predict the outcomes of TBM, and these are used in the evaluation of different treatment regimens (10).

Diagnosis of Pulmonary and Extra Pulmonary Tuberculosis

Methods for Diagnosis of Pulmonary TB

Radiologic Evaluation: Though radiologic evaluation does not provide an independent conclusive diagnosis of the disease and has to be followed by the sputum testing. If the coughing last for 2 weeks or more time and there is a severe high fever with sudden weight loss, then the person should be evaluated for TB. A chest X-ray is the foremost and the primary approach of evaluation of the suspected individual. The results of the radiological presentation of tuberculosis may vary but mostly they are specific and characteristic. This technique is very useful in order to monitor the complications and also suggests the management of the infection and the further follow ups required for the patient. Though chest X-ray is a valuable and useful diagnostic approach for pulmonary TB but it is not very specific.

AFB Smear Microscopy (Acid-Fast Bacilli) and Culture: For diagnosing the pulmonary tuberculosis, sputum is considered to be the most important sample. There is availability of the procedure implementing the direct sputum smear microscopy in nearly all the medical laboratories and health care facilities; however this process is rather expensive and inconvenient for those patients who have to make multiple visits to the hospital for submitting the multiple sputum samples in

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subsequent days. Though, the good quality of microscopy of two specimens has depicted the identification of vast majority of the smear-positive tuberculosis patients. Nonetheless, according to the revised policies of the World Health Organization, there were recommendations on both reducing the number of specimens from three to two for TB diagnosis and suitable external high quality assurance (19).

Molecular Methods

Nucleic Acid Amplification Test: This test is regarded as the most reliable and accurate test used in diagnosis with high efficiency and specificity but due to a very low sensitivity it is difficult to diagnose the disease especially in case of smear negative disease. In comparison to the AFB smear microscopy, the worth of the nucleic acid amplification test lies in the 1. Greater value of PPV (Predictive Positive Value) i.e. more than 95% with AFB smear positive specimens in which nontuberculous mycobacteria are common (NTMs) 2. and its confirmation for the presence of the *Mycobacterium tuberculosis* in 50 to 80% of the AFB smear negative, culture positive specimens (19).

Other Molecular Methods

- Line probe assay
- Xpert MTB/RIF (Cepheid)

Diagnosis of Extra Pulmonary Tuberculosis

- **Mycobacterial Stain And Culture**

Though, it is a challenging diagnostic test which requires obtaining the samples from the patient. However obtaining samples clinically from inaccessible sites may decrease the sensitivity of the diagnostic tests. Though the conventional method of the smear microscopy has a low sensitivity range of about 0 to 40%, negative results however cannot exclude the presence of tuberculosis. Whereas the results of the mycobacterial culture vary about 30 to 80%, but is requires a long duration of 2 to 8 weeks which is a very slow process in order to make any treatment decisions(23).

Treatment: Over the past recent years, the strategies implemented for the treatment of all forms of tuberculosis have changed. Especially with the introduction of two new drugs in the market; **bedaquiline** and **delamanid** and the new clinical

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trials have been undertaken and used radically in order to take care of people presented with all types of tuberculosis. Not only will these research studies will help to endeavor better methods of curing the infection but will also help to understand the different aspects of pathophysiology that can be used to achieve the targeted therapies to treat patients presented with various complications and types of tuberculosis.

Uptill now, there are no major changes made in terms of drug-susceptible tuberculosis. The standard treatment of tuberculosis still consists of the four drugs known as: rifampicin, isoniazid, pyrazinamide, ethambutol which is given to the patients for a continuous of two months period and is followed by the treatment of additional four months by two drugs; isoniazid and rifampicin. Reports from a 2014 study have depicted that difficult to treat phenotype, defined by high smear grades and cavitation has been indicated to require an additional time period of six months treatment. According to studies it has been shown that the administration of therapy on daily basis has result in improved outcomes of the treatment compared to treatment performed thrice a week. The advances in the therapeutics for treating drug-susceptible tuberculosis have focused on the treatment with a high dosage of rifampicin accompanied by fluoroquinolones used as an addition or substitution included in the treatment regimen. Though the administration of the high dose rifampicin has shown promising results in shortening and suppressing the complications of the disease whereas, the controlled trials using fluoroquinolones have not shown any such benefits. Many researches are ongoing in order to evaluate shorter tuberculosis treatment regimen including drugs: clofazimine, rifapentine and the new drug; bedaquiline.

Up till now, the forms of tuberculosis resistant to isoniazid have been considered to be the most common forms of drug-resistant tuberculosis around the globe. Although there are no guidelines on when to systemically test people presented with such case but with the advancement in the molecular tests for diagnosis, it is predicted to diagnose isoniazid resistant tuberculosis in near future. In accordance with the WHO recommendations, it has been suggested to give fluoroquinolones to patients with isoniazid-resistant tuberculosis.

The treatment regimen for rifampicin-resistant tuberculosis has been substantially

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changed due to the introduction of various novels repurposed drugs especially bedaquiline and delamanid and use of repurposed drugs known as clofazimine and linezolid. WHO has recommended using all oral therapy to treat rifampicin-resistant cases

These advances in therapeutics have greatly improved the treatment of such cases accompanied by various ongoing trials to study the various repurposed drug (3).

Novel Repurposed Drugs For Treating Rifampicin-Resistant Tuberculosis

- Bedaquiline
- Delamanid
- Pretomanid
- Linezolid
- Sutezolid
- Clofazimine
- Carbapenems

Conclusion

Due to its complicated pathogenesis, wide range of clinical manifestations, and challenges in diagnosis, tuberculosis continues to be a significant global public health concern. Disease control, lowering transmission, enhancing patient outcomes, and ultimately minimizing its impact on global health all depend on a thorough understanding of disease mechanisms, prompt and accurate diagnosis, and efficient treatment approaches.

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