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A CRITICAL REVIEW ON TUBERCULOSIS WITH ITS DIAGNOSIS AND TREATMENT

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ABSTRACT

A serious threat to humanity's survival is tuber-culosis (TB), which has resurfaced in areas where it had been assumed it had been eradicated over the previous three decades. New diagnostics, new vaccines, & new treatments are urgently needed to control the worldwide pandemic, but the lack of knowledge of the Mycobacterium tuberculosis (Mtb) is a major barrier to the creation of these control tools. It is our goal in this review to summarise the recent advances in our understanding of Mtb biology, with an emphasis on latent infection. There will also be a discussion of the types of EPTB extra pulmonary tuberculosis and PTB [pulmonary tuberculosis] the diagnosis & treatment of illness in certain populations.

Keywords: Tuberculosis, mycobacterium tuberculosis, CNS tuberculosis

INTRODUCTION

Although Tuberculosis is among the world's oldest & fatal disease, it continues to pose a significant health, societal, & financial impact on poor & intermediate nations worldwide, particularly in Africa [1]. An effective vaccine, lengthy drug regimens, limited tools for diagnostisin nations where Tuberculosis is prevalent, dismantling of health systems&measures to control which has so efficiently contributed for controlling Tuberculosis through-out major part of the twentieth century, have all helped lead to its reemergence as a global pandemic in the last decade or two. In the last two decades, health authorities&governments have rekindled their focus on tuberculosis (TB), leading to a reduction in TB-related fatalities by half. A deeper knowledge of the pathogenic mechanisms linked with infection&disease is commonly regarded as a prerequisite for developing effective tools for defeating this scourge. Although R. Koch's foundational work on Tuberculosis more than a century ago emphasised the illness's importance, we still don't know much about the pathophysiology of Tuberculosis or the immunological correlates, if any, that prevent people from contracting the disease, as posed by E.L. Trudeau more than a century ago [2].

HISTORY

Since ancient times, several civilizations have reported on cases of tuberculosis (TB) or illnesses that resemble it. As early as the Vedas, Tuberculosis was referred to as Yakshma, which means "wasting illness" in Sanskrit. TB-like sickness is described in ancient Greek, Chinese,&Arabic texts as well.[3] 150 million years ago, there were two Mycobacterium species on Earth. Mummies from Egypt'sPeru's pre-Colombian era &pre-dynastic era have typical tubercular spinal lesions. The earliest evidence of tuberculosis (TB) in humans was identified in a five hundred year-old skull which was found in turkey. Evidence of human tuberculosis dating back to the Neolithic period is strongest in a Neolithic newborn&women from a 9k-year-old hamlet in Eastern Europe. Tuberculosis was initially suspected to be infectious by Galen (131e201). GirolamoFracastorius (1483–1553) was the first to demonstrate that some illnesses might be spread by 'particles,' whether through direct or indirect contact between individuals. Miliary tuberculosis was originally described by Thomas Willis in 1621. Tuberculin was initially isolated from huge bacillus cultures by Calmette&utilised in a therapy known as "tuberculinisation," which was unsuccessful as a treatment for tuberculosis (TB). An intradermal skin test, devised by Charles Mantoux&used to diagnose TB, also made use of Tuberculin. Later, the Mantoux test [4]was given its current name in honour of Charles Mantoux, the inventor of the intradermal skin test. In his idea of 'contagious living fluid,' Benjamin Marten (1690e1752) proposed that Tuberculosis is produced by 'wonderfully minute living beings'. The transmission of tuberculosis (TB) from people to animals&from animals to humans was first proven by French army doctor Jean Antoine Villemin (1827e1892). 'Tubercula' is a Latin term that refers to the'small lump' present in all kinds of tuberculosis[3,4]&was suggested by Johann Lukas Schonlein in 1834. 15 On March 24, 1882, during a meeting of the Berlin Society of Physiology, Robert Koch stated that he had found the causal agent responsible for pulmonary tuberculosis&dubbed it "tuberkel virus." Robert Koch was awarded the Nobel Prize in medicine in 1905 for his work on Tuberculosis bacilli staining&growing on solidified cow or sheep serum. To create a vaccination against tuberculosis, scientists Leon Charles Albert Calmette (1863–1933)&Camille Guerin (1872–1961) subcultured Mycobacterium bovis 200 times in a Guinea pig model during 1908–1921. 'The schedule of tuberculosis,' written by Professor ArvidWallgren of the Royal Caroline Medical Institute in Stockholm, helped researchers

better comprehend the progression of tuberculosis.To combat tuberculosis in the 1940s, antitubercular medications including Streptomycin, PAS,&Isoniazid were discovered to be highly successful. It remained thought that tuberculosis (TB) was no longer a public health issue in the industrialised nations by the end of the 1970s.

Mycobacterium

Mycobacterium tuberculosis Belongs to ORDER- Actinomycetales CLASS- Actinomycetes FAMILY- Mycobacteriaceae GENUS- Mycobacterium

- Mycobacteria –respire in presence of oxygen, do not form spores, non-motile
- Shape straight rods or a littlecurled
- Size 0.2-0.6 micro metre by 1-10 micro metre
- morphology of Colony diverges from species to species, ranging from smooth to rough &from pigmented to non-pigmented (carotenoid pigment)
- Cell wall is made up of N-acetyl muramic acid having High content ofMycolic acid (70-90 c atoms)-renders acid fastness
- DNA High G þ C content (62-72mol %)
- Generation time Slow- ranging from 20 hours to 36 hours for Mycobacterium Tuberculosis

TYPES AND FEATURES OF TUBERCULOSIS

Tubercular Lymphadenitis

It has been known as Scrofula or the King's evil since ancient times. Nearly three-quarters of all instances of EPTB are caused by it. In 70-80% of instances of tuberculous lymphadenitis, the lymph nodes in the neck&axilla are affected. Ghon's complex or tonsils, adenoids, or sinonasal/osteomyelitis of the ethmoid bone infection can disseminate bacilli to the cervical lymph nodes. When MTB bacilli infect lymph nodes, they cause significant hyperemia, necrosis,&caseation of the lymph nodes they infect. Swelling of the surrounding nodes, as well as their adherence to the skin, causing them to burst through the skin&create sinuses; Compression of major blood arteries, recurrent laryngeal nerves (phrenic&laryngeal), or erosion of the bronchus are all possible side effects of mediastinal lymphadenitis (MLA).

It appears as a non-painful swelling in the neck (supraclavicular fossa). The procedure is often bilateral,&as the illness progresses, the lymph nodes merge&mat. As a result of the

ensuing inflammation of the skin above, an enlarged lymph node eventually ruptures, generating a sinus tract. Atelectasis can be caused by intrathoracicadenopathy, which can compress the bronchi or bronchiectasis (which is more frequent in children).[15,16]

Pleural Tuberculosis

Accounts for 30% of all cases of EPTB in countries with a high burden. Acute febrile sickness, nonproductive cough, pleuritic chest discomfort, night sweats, chills, weakness, dyspnea,&weight loss are all common symptoms in these patients. In the case of pleural TB, the pathophysiology is thought to be related to delayed hypersensitivity rather than direct pleural space infection. Neutrophils predominate the immune response in this area, which is afflicted by lung parenchymal diseases (first 24 hours). Adenosine Deaminase is released as a result of a lymphocyte-driven immunological response, resulting in the development of pleural granuloma (ADA). For the first 24 hours, neutrophils are the first line of defence, followed by macrophages, which peak at 96 hours,&finally lymphocytes. MTB can only be contained with a robust Th1 response. IFN-gamma is released by activated CD3&CD4 Th1 cells, which in turn activate macrophages to lyse MTB in response to IFN-gamma. IFN-gamma, interleukin-12 (IL-12),&increased helper T cells in pleural fluid support the Th1 immune response in pleural tuberculosis. Due to this delayed hypersensitive reaction, the pleura becomes more permeable. This in turn leads to an increase in fluid volume in the pleural space. Stomata are the apertures in the parietal pleura where the fluid drains. The collection of pleural fluid is caused by the diffuse involvement of the parietal pleura with tuberculosis&the destruction or blockage of stomata. Once chronic Tuberculosis empyema has been resolved, the pleura becomes thicker, scarred&calcified, producing persistent chest pains, dyspnea,&decreased lung capacity. In pleural tuberculosis, a well-known complication, pleural fibrosis has been recorded in 55% of cases.[5,6]

Abdominal Tuberculosis

Patients with extra pulmonary tuberculosis [EPTB] are diagnosed with abdominal tuberculosis in 11% of cases, compared to 55% to 90% in the era prior to effective ATT. Because of the following causes, the ileocecal area is the most typical location of gastrointestinal tract involvement.

- There is more lymphoid tissue (Peyer's patches) around
- An increase in the body's stasis response

- A greater increase in the rate of hydration&electrolyte absorption
- a lack of digestion

Colon, jejunum, appendix, duodenum&rectum are the other sites of involvement in decreasing order. Patients with impaired immune systems are more likely to develop hepatobiliary, pancreatic,&splenic tuberculosis. There are two ways that MTB bacilli enter the gastrointestinal organs&cause sickness by reactivating a dormant focus. Due to primary lung infection in children&as part of miliary tuberculosis dissemination. It is transmitted to the mesenteric lymph node by contaminated food or milk, where it remains latent in Peyer's patches.[7,8]

TB of Central Nervous System

A severe&frequently deadly type of EPTB, it mostly affects children under the age of five. Toxic Tuberculosis of the brain is a thorny problem. There are two primary varieties of this phenomenon.

- 0.5% of instances of Tuberculosis meningitis occur in children.
- Up to 40% of all brain cancers are caused by intracranial tuberculoma.

Dissemination of MTB bacilli into the central nervous system occurs during active pulmonary illness. A caseating focus in the brain parenchyma or meninges is caused by infectious monocytes/neutrophils crossing the Blood Brain Barrier (BBB). The phrase "Rich foci" refers to these types of foci. Later, the subarachnoid space is ruptured by these foci, causing an inflammatory T cell response&high levels of INF g&TNF-a in the CSF. This causes inflammation. Vasculitis&inflammation lead to infarction, which can cause irreversible cerebral damage&restrict CSF outflow, resulting in hydrocephalus[9]

Clinical feature

Due to the fact that Tuberculosis may affect the mouth, anus,&even lungs, how patients appear with the disease is quite variable. Symptoms include abdominal discomfort, a palpable mass,&maybe weight loss, fever,&appetite loss, with the terminal ileum or caecum being the most prevalent sites of involvement. The characteristic symptoms of tubercular peritonitis include a doughy belly, ascites, abdominal discomfort,&a high temperature. Dysphagia, odynophagia,&retrosternal pain/discomfort are all possible indications of esophageal TB.[17,18]

Additionally, the patient has a broncho-esophageal fistula/hematemesis that is life-threatening. Because of the acidic pH, lack of lymphoid tissue in the mucosa,&quick stomach emptying, gastric Tuberculosis is extremely rare. Dyspepsia, blockage of the duodenum,&ulceration of the duodenum are all symptoms of duodenal TB. Fistulae&blockage jaundice have also been mentioned as possible side effects of the procedure. Hematochezia, followed by constitutional symptoms&complications, is the most prevalent sign of rectal tuberculosis. Anal fissures, fistulae,&perirectal abscesses may also be seen.

Tuberculosis OF joint&bone

Of all EPTB cases, 10 to 15% are caused by this virus. During bacteremia of primary lung infection, latent MTB bacilli in any bone (spine or major joints) are reactivated, resulting in this condition.

For whatever reason, because to the abundance of blood vessels in these bacilli, they prefer the spine&big joints. Tuberculous arthritis occurs when the primary infection focus shifts from the bone to the joint. Batson paravertebral vein plexus&paraaortic lymph nodes are two places where bacilli can go from the lungs to the spine. It has been suggested that osteoarticular Tuberculosis can be caused by non-tuberculous mycobacteria (NTM) after a traumatic injury or a surgical operation such as joint arthroplasty. Patients with AIDS or organ transplant recipients are at risk of developing NTM bone infection because of hematogenous spread. Intravesical BCG vaccination treatment has been linked to M. bovis skeletal infections in recent years[10].

Genito-urinary Tuberculosis (GUTB)

All EPTB patients&between 2–5 percent of PTB cases are affected by it. In kidney transplant recipients, it occurs 20 times more frequently than in the general population.[11] Bacteria from the active site of infection (typically the lungs) travel hematogenously to the kidneys, where they create metastatic lesions (tubercles). These infection foci may heal on their own, grow&burst into nephrons, or remain dormant for many years, depending on the therapy.

In most cases, infection spreads from kidney to other genito-urinary organs in a downward spiral. Between the 2nd&4th decades of life, it commonly occurs after an initial lung infection for 5 to 25 years of inactivity.[12]

Immunology

Robert Koch (1880) used mycobacterial samples to show a delayed hypersensitive reaction in Guinea pigs&humans. In the tuberculin test, Seifert (1934) employed a pure protein derivative (PPD) he developed from the MTB extract he purified. M. Chase established in 1945 that immunity to MTB could only be given to animals by CD4 T cell transfer rather than immune serum. The role of T lymphocytes in protecting against MTB has now been established. Proximal draining lymph nodes contain dendritic cells (DCs) that help prime naive T lymphocytes. Airways, arteries,&loose connective tissue are all under the watchful eye of DC. Entrance is gained through binding to receptors on DC by the mycobacterial lipoglycanlipoarabinomannan (LAM). Toll-like receptor-2 (TLR-2) is activated by the lipoid adjuvant of LAM to activate antigen presenting cells (APC) (TLR-2). Both DC&APC eventually activate T lymphocytes,&memory CD4&CD8 cells play a crucial part in the immune response to MTB thereafter. Intercellular MTB can be killed by secreting cytolytic chemicals (e.g. granulysin, perforin)&chemokines from activated CD4&CD8 cells (e.g CCL5 which attracts infected macrophages).

Innate immunity protects against MTB by using natural killer (NK) cells as a bactericidal agent. The activation of NK cells does not require APCs&also enhances the activity of gamma delta T cells. Like macrophages, gamma delta T cells are mycobactericidal&INF-gamma secretors. All other resting macrophages/monocytes are activated by the production of IFN gamma, TNF- a,&Interleukin-2 from activated T cells. TNF, hazardous oxygen species,&nitric oxide are all upregulated by gamma IFN in macrophages. Granuloma development&efficient MTB confinement inside granuloma are caused by these.[13]

Histology

As a pathognomonic lesion in PTB&EPTB, tubercles can be seen at any location of infection. It's a typical granulomatous inflammatory response from the host's cell-mediated immunity to MTB bacteria. They start out as tiny&grow into macroscopically noticeable granulomas because of this process. Macrophages contain MTB bacilli, alveolar exudate rich in fibrin, lymphocytes,&multinucleated giant cells, all of which are encased in fibroblastic rims within granulomas. Non-caseating&caseating granulomas are both present in the granulomas generated.[14]

DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

Microbiological, cytopathological, or histological evidence of M. tuberculosis bacilli is required for a definitive Tuberculosis diagnosis. 2 Traditionally, mycobacterial infections are diagnosed in the laboratory by examining the phenotypic characteristics of colonies grown on LowensteineJensen media (LJ). Currently, quick mycobacteria identification is recommended to include both phenotypic&molecular assays, notably for the detection of Mycobacterium tuberculosis [19]. Mycobacteria can be detected using both direct&indirect methods in order to accurately diagnose EPTB. [20]

Acid fast staining – Because of their high lipid content, mycobacteria's cell walls have the unusual capacity to attach the Fuchsin dye&prevent it from being removed by acid alcohol. Acid fast bacilli (AFB)&other symptoms such as weight loss, fever&night sweats aid in the early detection of lung disease.

- Ziehl-Neelsen
- Kinyoun
- Fluorochrome staining [19]

Diagnosis of tuberculosis by culture isolation of M. tuberculosis from clinical samples is considered the "gold standard". More bacilli (10e100 bacilli/ml of concentrated material) may be identified using culture techniques, making them more sensitive,&they offer the isolates needed for traditional drug susceptibility tests&species identification[21-24]. The sensitivity of culture for detecting M Tuberculosis in extrapulmonary specimens varies from 0% to 80%. 9,43e45 To grow M Tuberculosis on solid medium like LJ media, it typically takes 4-8 weeks [25]. There are other conventional&molecular methods also which majorly contains PCR [polymerase chain reaction], line probe assay, pigment production, DNA sequencing etc. that can be used to diagnose the presence of disease

Treatment

Everyday regimens for drug-sensitive Tuberculosis in PLHIV, Pediatric Tuberculosis patients,&104 districts have been implemented by the RNTCP (formerly known as the National tuberculosis elimination programme). Tuberculosis patients with drug-resistant Tuberculosis are given an intensive phase of 8 weeks with Isoniazid (H), Rifampicin (R), Pyrazinamide (Z),&Ethambutol (E) in daily doses as per four weight band categories, while

the other three drugs are continued in the continuation phase (CP) for another 16 weeks as daily doses.Only during the first 8 weeks of IP treatment with Isoniazid, Rifampicin, Pyrazinamide, Ethambutol,&injectable Streptomycin, compared to the 20 weeks of CP treatment with Rifampicin, Isoniazid,&Ethambutol for previously treated cases of TB.Cases of multidrug-resistant/resistant Tuberculosis (MDR/RR-TB):Pyrazinamide,Kanamycin, Ethionamide, Cycloserine, Levofloxacin Isoniazid &Ethambutol are used for 6e9 months of intravenous (IP) treatment, followed by 18 months of daily intravenous (CP) treatment with Levofloxacin, Ethionamide, Cycloserine, Ethambutol&Isoniazid.

WHO included bedaquilline (Bdq), a diarylquinoline family medication that blocks MTb's ATP synthase energy source, to the MDR Tuberculosis regimen in 2015.DR-TB treatment in India has been made possible by the introduction of Delamanid (Dlm), a nitrpimidazole class of drug that inhibits mycolic acid synthesis&releases nitric oxide upon MTb metabolism poisoning, after many conferences and consultations with Indian government officials, the WHO country office in New Delhi, and other key development partners.

CONCLUSION

Tuberculosis has been around for almost a century,&Robert Koch's remarks, "amidst the persistently vast variation in ways&means of battling tuberculosis, it is nonetheless vital to inquire what measures do actually best fit the scientific standards," still ring true.Every aspect of tuberculosis diagnosis&treatment is a challenge to today's doctors, pathologists,&microbiologists,&the dilemma endures to this day. WHO's END Tuberculosis plan aims to reduce tuberculosis fatalities by 95% by 2035, which necessitates a full understanding of the disease&a systemic filling of detection&treatment gaps throughout the country. The wisdom of the past&the might of today's medicine will allow us to defeat this old enemy in all of its guises. A real attempt to raise public knowledge regarding tuberculosis is made in these review articles.

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