Innovations

Oral Complications of Tuberculosis – A Review

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Abstract: *Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, primarily affects the lungs but can also involve the oral cavity, though this is rare (1.4% of cases). Oral TB, often secondary to pulmonary TB, manifests as non-healing ulcers on areas like the tongue, palate, and lips. Diagnosis involves chest X-rays, sputum culture, and molecular tests. Oral pathologists play a crucial role in differentiating TB from conditions like syphilis, fungal infections, and squamous cell carcinoma. Treatment follows systemic TB protocols, including anti-tubercular drugs and the DOTS strategy for compliance.*

Keywords : *Tuberculosis, Mycobacterium tuberculosis, oral TB, DOTS.*

Introduction

Tuberculosis (TB) is a chronic granulomatous disease. Though multifactorial, it is primarily caused by bacteria Mycobacterium tuberculosis. Although, TB mainly affects the pulmonary system, it can be manifested in other regions of the body (extrapulmonary) including oral cavity. Oral TB can be either a primary lesion; or secondary to the underlying pulmonary TB based on the World Health Organization

(WHO) 2016 reports, about 10.4 million new cases and 1.8 million deaths occur globally every year [1].India is among the six ‘‘high-burden countries’’ that comprise 60% of total TB cases. Oral TB is a rare entity accounting for only 1.4% of total cases. But currently, tuberculous oral lesions are reemerging along with other extrapulmonary manifestations as an outcome of drug-resistant TB and acquired immunodeficiency syndrome [2].

Generally, tuberculosis can be classified into two types, i.e. primary and secondary tuberculosis or postprimary tuberculosis. Primary tuberculosis is the first stage when the infected individual first contact with Mycobacterium tuberculosis, secondary tuberculosis or post-primary tuberculosis occurs several months or years after primary infection usually caused by compromised host immunity induced by HIV infection and poor nutrition [3].

Transmission of TB is by inhalation of airborne infectious droplets from persons with active pulmonary TB when they cough, sneeze or speak. Extrapulmonary active TB, affects parts of the body such as the mouth, from which Mycobacterium tuberculosis can be transmitted by direct contact. Oral tuberculosis often occurs due to the spread of bacteria through oral mucosal breaches from ulcers, minor injuries, infected sputum, or hematogenous dissemination from other infected areas[4].

Etiology & Pathogenesis of Oral Tuberculosis

The micro-organism to cause Tuberculosis is acid-fast bacteria Mycobacterium tuberculosis, that is rod-shaped bacteria, aerobic, thin, non-encapsulated, with length of 2-5 μm and 0.2-0.5 nm width. The discovery was initially made by Robert Koch in the year 1882. The acid and alcohol-resistant bacillus of Mycobacterium tuberculosisare transmitted via droplet nuclei through the air and these multiply in the pulmonary alveoli. These micro-organisms replicate in alveolar macrophages and spread through the regional lymph nodes. In this process, T-helper cells (CD4) activate macrophages through secretion of cytokines, interleukins and interferon-gamma in which the infection gets suppressed (primary infection), or they can remain latent to reactivate in later stages of life when immunity is disturbed[5]. If the host immune response is low and fails to prevent the replication of the bacteria, the disease gets reactivated. About 5-10% of patients who are exposed develop an active TB in some point in their lifetime, and this becomes secondary tuberculosis. In contrast with primary tuberculosis, the lesions of secondary infection are chronic and do not recover spontaneously. Tuberculosis can affect any part of the human body including the oral cavity.

Human oral cavity produces saliva that serves as the cleansing agent with its anti-bacterial properties so the micro-organisms cannot get through the epithelium walls[6].However, these micro-organisms can get access to the underneath connective tissue through the epithelium trauma. The occurrence of infection is

based upon systemic factors including poor host immunity and the increased virulence of microorganisms. Apart from mycobacterium tuberculae, local predisposing factors in the mouth that can lead to oral tuberculosis comprise of: local trauma, poor oral hygiene, presence of previous lesions such as cysts, abscesses, fractures of the jaw, and periodontitis[6].

Immune response of the host to M.tuberculosis

Mycobacterium tuberculosis is generally transmitted through aerosols and establishes infection in the lung. Initially the bacilli invades alveolar macrophages and dendritic cells. Mycobacterium tuberculosis survives and replicates within these cells. If the host immune response is good, Immune mediators such as interferon-gamma (IFN-γ) activate macrophage and promote bacterial killing. (IFN-γ) is secreted by natural killer (NK) and T cells upon instruction by interleukin 12 (IL-12) and interleukin 18 (IL-18) produce by dendritic cells (DC) and macrophage. DC become activated through Toll-like receptor (TLR) signal and migrate to the lung lymph node to initiate an immune responsei.e. activation of T cells. Mycobacterial ligands for TLRs promote inflammation that causes the release of chemokines and inflammatory cytokines. IL-12 along with IL-18 induces NK cell activity and biases the immune response toward a T helper 1 cells (Th1) profile characterised by interferon-γ (IFN-γ) production. IFN-γ activates macrophage to express microbicidal cytokines, of which tumour necrosis factor alpha (TNF-α) mainly induces mycobacterial infection and formation of granuloma [7]. Formationof granuloma generally represents a host strategy to contain the infection and limit the spread of infection. Simultaneously, granulomas can cause pathological damage through caseous necrosis, by hematogenous or lymphogenousspread and also the infection may become extra pulmonary TB (EPTB). If it occurs in the mouth,it is called oral tuberculosis. Though Mycobacterium tuberculosis in the oral fluid of people with pulmonary TB is a common finding, butoccurrence of oral tuberculosis is uncommon. This might be due to protection provided by intact oral epithelial barrier against Mycobacterium tuberculosis penetration, and to the anti-bacterial properties and the cleansing action of the saliva. Oral tuberculosis is a rare finding i.e. 0.1% - 0.5% of people with pulmonary TB will develop secondary oral TB. Tissues mainly affected by Oral tuberculosis includethe tongue, followed by the palate, the lips, the buccal mucosa, and the gingiva. It usually appears in the form of non-healing ulcers, and may also occur as nodules, granulomata, or fissures, or as ulcers with indurated undermined margins, and a necrotic base[8].

General symptoms and Oral complications

Tuberculosis usually affects pulmonary tissue, the main symptoms that it causes are productive cough, fatigue, weight loss, anorexia, mild fever and night sweats. Cough

is generally dry at first but then a productive form of purulent sputum is observed and often it is accompanied with blood[4]. In the oral cavity, tubercular lesions are rarely found, but 0.1-0.5% of patients with pulmonary tuberculosis have been noted to have oral lesions of secondary tuberculosis. The most common sites affected are tonguethat is followed by palate, lips, buccal mucosa, gingiva, and alveolar bone. Lesions are mainly found in the form of ulcers and 50% of them occur on the tongue. These usually appearas shallow, oval, indolent, yellow-gray lesions with a clear edge[9].These can be found on any part of the tongue including tongue tip, lateral margins, dorsum, and base of the tongue. Lesions of the oral mucosa appear in the form of ulcers caused due to caseationnecrosis in infected tissues. Palatal lesions are in the form of small and painless ulcers that are mostly found on the hard palate. Gingival lesions containgranulation tissue. Also, lesions can also be associated with marginal periodontitis. Oral tubercular lesions are mostly painless and enlarged lymph nodes might be the common finding[10].

In most cases, lesions on the lips usually present as small ulcers with indurated margins. Tuberculosis can also affect maxilla and mandible, that can lead to osteomyelitis. The mandible is morefrequently involved than maxilla [11].Trismus, paresthesia and regional lymph node enlargementare the main features. Involvement of the maxilla and mandible occurs due to expansion of the gingival and periodontal lesions or after teeth extraction that affected by tuberculous granulomas or metastasis of lung tuberculosis through either hematogenous orlymphatic [12].Periapical involvement and post-extraction socket with tuberculosis infection have also been reported that can lead to tooth loss and eventually, the post-extraction sockets are filled with large mass of tubercular granulationtissue [13].

Diagnostic considerations

Chest X-rays (CXR) play a crucial role in tuberculosis (TB) diagnosis, helping to differentiate primary TB from secondary TB but it do not provide an etiological diagnosis or detect latent TB infections[14]. For early detection, microscopic examination using stains like Ziehl-Neelsen (ZN) is essential, detecting 60-70% of culture-positive samples with a sensitivity threshold of 5 x 10^3 organisms/mL. Fluorochrome stains such as auramine and rhodamine offer improved sensitivity, rapid results, and cost-effectiveness compared to ZN staining, particularly enhancing detection rates in clinical specimen [15].

Sputum culture is a highly sensitive diagnostic method for detecting Mycobacterium tuberculosis (MTB. Traditional culture methods, like the Lowenstein-Jensen (L-J) medium, take over two weeks to yield results, delaying treatment initiation. Recent advancements, including DNA probes, high-performance liquid chromatography

(HPLC), and rapid methods like the radiometric BACTEC system, have improved the speed and accuracy of TB diagnosis[16].

Immunological methods such as the Tuberculin Skin Test (TST) commonly employed for tuberculosis screening. The TST, also known as the Mantoux test, involves injecting PPD tuberculin intradermally and assessing for induration (≥ 5 mm indicating a positive result) after 48-72 hours. It's simple but requires skilled personnel for administration and interpretation. TST's sensitivity is lower in immunocompromised individuals and it yields false positives in BCG-vaccinated individuals or those with non-tuberculous mycobacteria infections. QFT, an interferon-gamma release assay is preferred in settings where TST follow-up might be challenging or among immunocompromised individuals. It measures cell-mediated immune response by analyzing IFN-γ release from blood samples stimulated with MTB antigens [17]. Molecular methods play a crucial role in diagnosing drug-resistant Mycobacterium tuberculosis (MTB) infections, especially in cases where traditional smear tests are ineffective. These methods offer rapid results, aiding clinicians in promptly initiating appropriate treatment. Techniques like polymerase chain reaction (PCR), strand displacement amplification (SDA), and loop-mediated isothermal amplification (LAMP) are utilized to detect specific MTB genes with high sensitivity and specificity. Line probe assays (LPA) like Genotype MTBDRplus further enable simultaneous detection of MTB and resistance to rifampicin, aiding in early management decisions [18,19].

Role of an Oral Pathologist

The role of an oral pathologist in diagnosing oral tuberculosis (TB) is pivotal, encompassing various challenges amidst overlapping clinical presentations with conditions like primary syphilis, deep fungal diseases, chronic traumatic ulcers, and squamous cell carcinoma. Detecting TB in oral lesions is particularly demanding due to the limited sensitivity of traditional methods such as acid-fast bacilli (AFB) staining (52%) and culture (58%), especially in lesions located on the lips and soft palate. However, nested or reverse transcription PCR methods significantly enhance detection rates, improving from 2-17% with culture to 89-100% with PCR. Despite these advancements, PCR may still struggle distinguishing between M. tuberculosis and M. bovis, complicating accurate identification. Microbiological identification is crucial for diagnosing oral TB and determining antimicrobial resistance, although multidrug-resistant strains are rare in oral TB patients. Resistance to antituberculous drugs can lead to treatment failure, especially in cases coexisting with oral cancer, underscoring the necessity for comprehensive diagnostic approaches. In navigating these complexities, excisional biopsies with bacteriological culture are often conducted to confirm TB, given the low positivity rate of acid-fast bacilli in oral tissues (7.8%). For lesions in the tongue, deeper biopsies are recommended to

ensure adequate sampling depth, given the risk of superficial biopsies missing underlying pathology [20].

Treatment

Treatment of oral tuberculosis the same as systemic tuberculosis involves the use of anti-tubercular drugs, typically including a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol for a standard six-month regimen. Treatment goals focus on rendering patients non-infectious, preventing morbidity and mortality, and averting drug resistance. For drug-resistant TB, second-line drugs and prolonged regimens are necessary. Directly Observed Treatment, Short-course (DOTS) strategy is often employed to ensure compliance and monitor response. Early and accurate drug susceptibility testing is crucial to tailor the treatment plan effectively[21].

References

1. *Kadar N, Namboodiripad A, Haris M, Divya R. Tuberculous Ulcer of Oral Cavity. Oral MaxillofacPathol J 2017;8(2):105-107.*
2. *Kurniawati A, Mertaniasih NM, Agil M. Proceeding The 1st IBSC: Towards The Extended Use Of Basic Science For Enhancing Health, Environment, Energy And Biotechnology 2020; 127-131.*
3. *Souza BC, Lemos VM, Munerato MC. Oral manifestation of tuberculosis: a case-report. Braz j infect dis 2 0 1 6; 20(2): 210-213.*
4. *Saluja P, Dave A, Arora M, Singhal I. Primary Oral Tuberculosis Imitating Malignancy- A Rare Case Report. Journal of Clinical and Diagnostic Research 2023; 17(1): 22-25.*
5. *Krawiecka E, Szponar E. Tuberculosis of the oral cavity: an uncommon but still a live issue. Postep Derm Alergol 2015; 32(4): 302-306.*
6. *Kim SY, Byun JS, Choi JK, Jung JK. A case report of a tongue ulcer presented as the first sign of occult tuberculosis. BMC Oral Health 2019; 19(67): 2-5.*
7. *Rattan V, Rai S. Tuberculosis of the Oral Cavity and Associated Structures: The PGIMER Experience. J Postgrad Med Edu Res 2013; 47(4): 214-217.*
8. *Gofur NR. Clinical Manifestation of Oral Tuberculosis in HIV Patient: A Review Article. Journal of Dental Science Research Reviews & Reports 2022; 4: 123.*
9. *Kumar RD, Udagatti VD. Tuberculosis of Tongue (Oral Cavity): A Case Report. Int J Head Neck Surg 2018; 9(4): 121-123.*
10. *Jain P, Jain I. Oral Manifestations of Tuberculosis: Step towards Early Diagnosis. Journal of Clinical and Diagnostic Research 2014, 8(12): 18-21.*
11. *Pavithra V, Nambiar S, Augustine D, Sowmya SV, Kumar KV, Prasad K, Rao RS. Oral Tuberculosis with Advanced Diagnostic Trends. World J Dent 2016; 7(4): 203-207.*

12. *Wang WC, Chen JY, Chen YK, Lin LM. Tuberculosis of the head and neck: a review of 20 cases. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2009; 107: 381-386.*
13. *McMurray DN Baron's medical microbiology textbook (online textbook) Galveston: University of Texas Medical Branch (2001).*
14. *Ba F, Rieder H. A comparison of fluorescence microscopy with the Ziehl-Neelsen technique in the examination of sputum for acid-fast bacilli. Int J Tuberc Lung Dis 1999; 3: 1101-1105.*
15. *Giampaglia CM, Martins MC, de Oliveira Vieira GB, Vinhas SA, da Silva T, Palaci M, Marsico AG, Hadad DJ, Mello FC, de Souza Fonseca L, Kritski A. Multicentre evaluation of an automated BACTEC 960 system for susceptibility testing of Mycobacterium tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2007;11(9):986-991.*
16. *Check W Latest TB testing guide set forth by ATS, CDC, IDSA CAP Today (2017).*
17. *Gholoobi A, Masoudi-Kazemabad A, Meshkat M, Meshkat Z. Comparison of culture and PCR methods for diagnosis of Mycobacterium tuberculosis in different clinical specimens. Jundishapur journal of microbiology. 2014 Feb;7(2).*
18. *WHO The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs. WHO, Geneva (2016).*
19. *Jain P, Jain I. Oral manifestations of tuberculosis: step towards early diagnosis. Journal of clinical and diagnostic research: JCDR. 2014;8(12):18.*
20. *Sierra C, Fortún J, Barros C, Melcon E, Condes E, Cobo J, et al. Extra-laryngeal head and neck tuberculosis. Clin Microbiol Infect 2000;6:644-648.*