Orofacial tuberculosis: Clinical manifestations, diagnosis and management

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Abstract

Orofacial tuberculosis (TB) is an uncommon form of extrapulmonary TB and is nonspecific in its clinical presentation. It can be misdiagnosed especially when oral lesions are present before systemic symptoms become apparent. Doctors especially attending dentist who generally is the first among clinicians to come across such pathological entity should be aware of the orofacial lesions of TB and consider them in the differential diagnosis of suspicious oral lesions to ensure early diagnosis of TB and its treatment. In this review, we have discussed in detail the clinical presentation of various forms of orofacial TB, diagnosis, and management of patients. Also, an update is provided about recent anti-TB drug development.

Keywords: Dentist, diagnosis, mycobacterium, oral tuberculosis, tuberculosis

Introduction

Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide[1] especially in developing countries where its prevalence is very high. The probable reasons for this are poverty, overcrowded shelters, lack in public health efforts to control TB, HIV infection epidemic and development of multidrug-resistant bacteria.[2] The BRICS group (Brazil, Russian Federation, India, China and South Africa) accounts for 46% of all incident cases of TB and 40% of all TB-related mortality.[3] India accounts for nearly one third of global burden of the disease.[4] Caused by *Mycobacterium tuberculosis* (MBT), the disease most commonly affects lungs but in 10-15% cases other parts of the body can also get affected, i.e. extrapulmonary TB.[5] Orofacial TB is an uncommon form of extrapulmonary TB and is nonspecific in its clinical presentation. It can be misdiagnosed especially when oral lesions are present before systemic symptoms become apparent. Doctors especially attending dentist who generally is the first among clinicians to come across such pathological entity should be aware of the orofacial lesions of TB and consider them in the differential diagnosis of suspicious oral lesions to ensure early diagnosis of TB and its treatment. In this review, we have discussed in detail the clinical presentation of various forms of orofacial TB, diagnosis, and management of patients. Also, an update is provided about recent anti-TB drug development.

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Discussion

Orofacial TB is a rare manifestation of extrapulmonary TB, occurring in approximately 0.1–5% of all TB infections.[6] It can be primary or secondary. Primary form is rare and more commonly found in children and adolescents.[7] In contrast, the secondary form is more common (0.005% to 1.5% of cases) and is usually seen in middle-aged and elderly patients.[8] Orofacial TB can involve any site of the oral cavity and associated structures such as tongue, palate, lips, oral mucosa, jaw bones, sinuses, temporomandibular joint (TMJ), etc. Recently, Andrade *et al.*[9] proposed a classification of orofacial TB [Table 1] based on the site involved.

The clinical presentation of various forms of Orofacial TB is discussed below in detail

Tuberculous ulcer

May present as single or multiple, superficial, or deep, painful or painless ulcers with an irregular border which tends to increase slowly in size. They usually develop as a small tubercle which then softens to form a shallow, ovoid ulcer with undermined margins and is lined with pale granulation tissue.[10] Tiny single or multiple nodules called "sentinel tubercles" may be seen surrounding the

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Table 1: Andrade's classification of orofacial tuberculosis

Type I	Lumpy jaw; mandible or maxilla is involved and extraoral swelling is present without intraoral or extraoral draining sinuses
Type II	Nonhealing extraction sockets with/without intraoral or extraoral draining sinus/sinuses
Type III	intraoral or extraoral draining sinus/sinuses in the orofacial region and an osteomyelitic bony lesion
Type IV	TB lymphadenitis of the head face neck region without any features of type I, II, III, or V
Type V	Lesion of other sites in and around the oral cavity, e.g., maxillary antrum, salivary glands, gingiva, orofacial muscles, tongue, etc.

ulcer. Tongue is most commonly affected. However, lesions also occur on floor of the mouth, gingiva, palate, and lips.[11] The differential diagnosis of a tuberculous ulcer of the oral cavity includes traumatic ulcers, syphilitic ulcers, aphthous ulcers and various carcinomas like squamous cell carcinoma, lymphoma etc.[12]

Tuberculous gingivitis

Tuberculous gingivitis may appear as nodular or papillary proliferation of gingival tissues which is diffuse and hyperaemic.[13] There may be absence of any clinical attachment loss, alveolar bone loss or significant cervical lymphadenopathy. Such diffuse gingival enlargements fail to respond to initial usual therapy consisting of supragingival debridement.[14] Sometimes tuberculous gingivitis can be seen simultaneously with marginal periodontitis and enlarged cervical lymph nodes[15] or may present as periodontal loss of tooth support leading to loose teeth and gingival enlargement.[4] A biopsy of the lesion is mandatory for arriving at the diagnosis of TB.

Tuberculous dental periapical granuloma

Tuberculous involvement of the periapical tissue has often been reported. Three routes can be perceived to be entry portals for the tubercle bacillus to become implanted in the periapical tissues. The first is the invasion of the dental pulp through a deep carious lesion by the acid-fast bacilli in the saliva. Should the pulp degenerate and breakdown, a tuberculous periapical infection might result. A second route is the hematogenous and third is the deep periodontal pocket. Patients not responding to the usual periodontal treatments may be harboring tuberculous infection of the paradental tissues even though its presence is not evident.[16] The lesions are usually painless and sometimes involve a considerable amount of bone by relatively rapid extension.[10]

Tuberculous involvement of extraction sockets of teeth

Healing of the tooth extraction sockets is delayed and the socket gets filled with "tuberculous granulation tissue" consisting of many pink to red elevations.[17] Outbreak of TB following dental extractions at two community dental clinics has been reported where 15 patients developed primary TB lesions, out of them 8 patients had primary tooth socket involvement. The dentist who performed the extractions at both the clinics was found to have active bilateral pulmonary TB.[18]

Tuberculous osteomyelitis of maxilla and mandible

Tuberculous osteomyelitis is rare and constitutes less than 2% of skeletal TB. Jaw involvement is even rarer.[19] The mandibular involvement is more frequent than maxilla and alveolar and angle regions have greater affinity.[20] Tuberculous osteomyelitis commonly affects the adults; however, in some cases children are also affected.[21] The spread of infection may be by direct transfer from infected sputum,[22] through an extraction socket or mucosal opening associated with an erupting tooth or by regional extensions of soft tissue lesions to underlying bone or by hematogenous spread.[19] Chapotel[22] described four clinical forms of TB of the mandible. The first is the superficial or alveolar form that involves the alveolar process, second is the deep or central form in which the angle of the mandible is involved, third is the diffuse form characterized by progressive extensive necrosis of mandible that might involve the TMJ and the fourth one is acute osteomyelitis form.

TB of the jaw causes slow necrosis of the bone and formation of a sub-periosteal abscess (lumpy jaw) appearing as a painless, soft swelling. This sub- periosteal abscess may burst resulting in single or multiple sinuses intraorally or extraorally. Pathological fracture of mandible or sequestration may also occur.[20] Diagnosis of tuberculous osteomyelitis is a significant challenge as the smears for acid-fast bacilli usually do not yield positive results.[23] Polymerase chain reaction or nucleic amplification assays may be helpful in obtaining an earlier diagnosis; however, a negative result does not rule out TB.[24] In the early stages, when plain radiographs appear normal, MRI or CT may help to localize lesions. The radiographic picture of tuberculous osteomyelitis usually presents as a blurring of bone details leading to diffuse radiolucent picture and cortical plate erosion. It can also present as mixed radiopaque–radiolucent appearance or "worm-eaten" appearance of bony lesions with fistulae formation through which small sequestra are exuded. The findings are similar to that of the destructive disease if the periodontal tissues get involved.[25] More advanced lesions may appear as osteoporosis, bone lysis, sclerosis and periostitis that mimic chronic pyogenic osteomyelitis and it is often difficult to differentiate the two conditions. Joint involvement may be present but unlike pyogenic osteomyelitis, articular margins and cartilage space are spared. A solitary lytic lesion can also appear sometimes which can mimic neoplasia.[26] A biopsy is mandatory for the diagnosis, and anti-TB drugs along with surgical debridement if required are the main mode of treatment.

Tuberculosis of maxillary sinus

TB of maxillary sinus is usually a disease of adults and remains an under-diagnosed entity. It is usually secondary to pulmonary or extrapulmonary TB resulting from the bloodstream or by direct extension.[27] Primary sinonasal TB is rare probably due to bactericidal secretion, ciliary movement and mechanical filtering by vibrissae of nose.[28] Most commonly, it presents as nasal discharge, stuffiness of nose, crust formation and sometimes with epistaxis.[29] It can also present as fluctuant swelling, i.e. Pott's puffy tumor and may resemble a malignant lesion. Three types

of sinonasal TB have been described: (i) Mucosal involvement leading to formation of polyps with minimal pus discharge, this type is more common; (ii) bony involvement and fistula formation with abundant discharge of acid-fast bacilli (AFB); this type can lead to midfacial defect; (iii) hyperplastic type has granuloma formation and mimics a malignancy.[30] If not treated early, it can lead to complications like brain abscess and deterioration of vision.[31] Antral lavage examination for AFB and culture for *Mycobacterium tuberculosis* can facilitate early diagnosis. The diagnosis of TB sinusitis is usually based on the absence of response to usual antibiotics, the presence of a caseous granulomatous inflammatory lesion and by bacteriological culture or polymerase chain reaction assay.[32] Sinus surgery may be required for sinus drainage and specimen collection. CT or magnetic resonance imaging can be helpful to figure out the extent of disease. Appearance of calcification in sinuses on CT scans can be indicative of sinonasal TB, and imaging findings are mostly nonspecific.[33] Anti-TB medication and/or surgical debridement is the mainstay of the treatment.

Tuberculosis of temporomandibular joint

TB of the TMJ is rare; only a few cases have been reported.[34-36] The low frequency reported in the literature might be due to missed diagnosis than to its real prevalence.[37] The clinical appearance of TB infection of the TMJ is unspecific and can resemble osteomyelitis, arthritis, cancer or any kind of chronic joint diseases.[34] Thus, TMJ TB should be considered in the differential diagnosis when the patients present with pain and stiffness of the joint[37,38] or with chronic joint diseases. The onset of symptoms is insidious: Nocturnal muscular spasm, leading to soft and elastic joint tumefaction, characteristically without erythema, with edema and leading early to severe and localized periarticular muscle atrophy. Subsequently, necrotic destructive phenomena occur, which de-structure the joint.[38] In the end stage of disease, fibrosis or bony ankylosis can develop. Diagnosis is usually made by culture, staining and imaging. MRI can detect intraarticular pus in the early stage of the disease when conventional radiological techniques are insensitive until bony changes develop.[39] MRI findings also show bone marrow edema and extra-articular cystic collections in osteoarticular TB.[40] In the advance stages, radiographic findings may show erosion of the condyle and glenoid fossa.[39] Exploration and biopsy are necessary to establish the definitive diagnosis. The treatment of the TMJ TB consists of conventional drug therapy. Surgical excision and decortication is done when intense pharmacotherapy fails.[34]

Tubercular sialadenitis

TB of the salivary gland is a rare condition even in countries like India, where the disease is rampant.[41] The most common salivary glands involved in primary TB are parotid glands, whereas in systemic TB submandibular glands are most commonly involved.[42] There are two clinical forms of tuberculous parotitis. The first is the localized form which is common and involves intraglandular/periglandular lymph nodes, while the other diffuse parenchymatous form is very rare and is considered to be an acute pathology involving whole of the gland. It may be secondary to the nodal infection.[43] Initially, mycobacterium manifests in the nodes of the preauricular area. It presents as slow growing, non-tender localized swelling in front and below the ear.[44] The pain, abscess, fistula, and facial nerve involvement are the late features. The constitutional symptoms of TB like chronic cough, fever, weight loss may be present but are rare.[45] The diagnosis of tubercular parotitis is very difficult because of the absence of symptoms and may often be misdiagnosed as a benign parotid tumor.[46] A detailed history, examination and FNAC have been advocated for the diagnosis of tubercular parotitis.[44] The Ziehl-Nielsen staining and culture for the mycobacterium is usually found negative. If the patient is not already known to have TB or another mycobacteriosis, the diagnosis is made by microscopy after excision of the gland. Polymerase chain reaction (PCR) should always be considered before surgical intervention to enable differential diagnosis of a salivary gland tumor.[47]

Tuberculous lymphadenitis

Tuberculous lymphadenitis in the cervical region, also known as scrofula,[48] is the most common site of extra pulmonary TB[49] and accounts up to 5% of the cervical lymphadenopathy.[50] It often affects children and young adults in age range of 30–40 years and shows female predilection.[51] It can present as a single or bilateral neck mass, affecting deep lymph nodes and may be associated with supraclavicular and axillary node involvement.[52] Patients present with slowly enlarging asymptomatic lymph nodes in the neck which is persistent. The mass is referred to as a cold abscess, due to lack of local color or warmth and the overlying skin presents a violaceous color.[53] Other symptoms of disease, such as fever, chills, malaise and weight loss, are present in about 43% of the patients.[53] As the lesion progresses, skin becomes adhered to the mass and may rupture, forming a sinus and an open wound. Fine-needle aspiration cytology (FNAC) and direct microscopic screening for acid-fast bacilli (AFB) are recommended for the routine diagnosis of tuberculous lymphadenopathy along with culture that remains the gold standard for diagnosis. Diagnosis often requires biopsy. Therapy includes various types of anti-TB chemotherapy, surgical excision, or a combination of surgery and chemotherapy.[53]

Lupus vulgaris

Lupus vulgaris is the most common form of cutaneous TB found in individuals with moderate immunity and high degree of tuberculin sensitivity.[54] It is caused by *M. tuberculosis* and can involve the skin by hematogenous or lymphatic route. Eighty percent of the lesions are on the head and neck[55] and most often on the face around the nose, eyelids, lips, cheeks, ears. Females are affected two to three times more often than males.[54] Lupus vulgaris skin lesions are of five types – (a) plaque, (b) ulcerative or mutilating, (c) vegetating, (d) tumor-like and (e) papulonodular.[56] The plaque form is the most common form of LV, accounting for 32% of cases, whereas ulcerative form is the most destructive and deforming of all lesions.[57] A single or several, unilateral, reddish-brown papules first

appearing on face, neck or arms and then coalescing into erythematous plaques. The surface of the papules exfoliates and the centers scar. Papules recur on the scarred areas, gradually and repeatedly enlarging and coalescing. This leads to the formation of large, firm, elevated plaques. At the periphery are small reddish-yellow or brown nodules.[58] The characteristic lesion is a reddish-brown plaque, composed of nodules which show an "apple-jelly" color when pressed with a glass spatula (diascopy).[59] The lesions may ultimately develop into disfiguring skin ulcers if left untreated. In long-standing scarred lesion, squamous cell carcinoma can develop.[60] Lupus vulgaris is diagnosed by the clinical features, pathology, and strong positive in tuberculin skin test. Identification of *M. tuberculosis* is made by PCR or culture. The disease treatment consists of systemic anti-TB drugs.

Apart from the above-mentioned oral manifestations, expectoration of the infected sputum may cause tuberculous tracheitis and laryngitis resulting in hoarseness, coughing, and pain, and tuberculous ulcers on the tonsils resulting in dysphagia.[61]

Summary of the orofacial TB manifestations is given in Table 2.

Diagnosis of tuberculosis

Step by step approach is shown in Table 3.

Treatment of orofacial TB

The treatment of orofacial TB is the same as standard antimycobacterial treatment regimens used for treating pulmonary TB. The five basic or "first line" antibiotics that form the core of TB treatment[68] are: Isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin. Second line or reserve drugs[68] are used when first-line drugs are not effective and consist of Group I first-line oral agents like pyrazinamide, ethambutol, rifabutin; Group II injectable agents like kanamycin, amikacin, capreomycin, streptomycin; Group III fluoroquinolones like levofloxacin, moxifloxacin, ofloxacin; Group IV oral bacteriostatic second-line agents like para-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide; and Group V drugs with an unclear role in the treatment of drug-resistant TB like clofazimine, linezolid, thiacetazone, amoxicillin/clavulanate, high-dose isoniazid, imipenem/cilastatin, clarithromycin. WHO recommended treatment regimens for TB have several inherent problems, making new anti-TB drugs and treatment regimens a clinical and public health priority.[69] New anti-TB drugs are being researched that should be affordable, have shorter treatment regimens, be more efficacious than existing drugs, should successfully treat MDR-TB, XDR-TB as well as latent TB and should also be compatible with antiretroviral drugs. After decades of quiescence in the development of anti-TB medications, two new drugs have been approved. The first novel drug bedaquiline for treatment of MDR-TB was approved in December 2012; it is also under clinical evaluation for the treatment of drug-susceptible TB, with drug regimens not containing rifamycins.[70] The drug is still in Phase III trials and WHO urges caution in its use and strict adherence to conditions listed in the WHO interim policy guidance issued in June 2013. Delamanid is the second drug that has been was granted conditional approval by the European Medicine Agency in April 2014 for the treatment of drug resistant TB. Several other novel compounds are being evaluated and are in various phases of preclinical or clinical trials. Some of them are tabulated in Table 4.

Conclusion

The orofacial TB can occur anywhere in the oral cavity and its associated structure and presents a non-specific clinical picture. Doctors should be aware of the orofacial lesions of TB and consider them in the differential diagnosis to ensure early diagnosis and management of TB as any delay may lead to serious consequences. Also, the general public should be educated about TB and its extra pulmonary manifestations and made aware that the disease is completely curable if managed properly. This will reduce the social stigma attached with the disease which leads

Table 2: Various manifestations of orofacial tuberculosis

Condition	Salient Features
Tuberculous ulcer	Shallow, ovoid ulcer with undermined margins and is lined with pale granulation tissue
Tuberculous gingivitis	Nodular or papillary proliferation of gingival tissues which is diffuse and hyperemic
Tuberculous dental periapical granuloma	Painless swelling and sometimes involve a considerable amount of bone by relatively rapid extension
Tuberculous involvement of extraction sockets of teeth	Delayed healing, the socket gets filled with "tuberculous granulation tissue" consisting of pink to red elevations
Tuberculous osteomyelitis of jaws	Lumpy jaw, intraoral or extraoral single or multiple sinuses may be present. Pathological fracture of mandible or sequestration may occur
Tuberculosis of maxillary sinus	Nasal discharge, stuffiness of nose, crust formation and sometimes with epistaxis
Tuberculosis of temporomandibular joint	Nocturnal muscular spasm, soft and elastic joint tumefaction, without erythema, with edema and severe and localized periarticular muscle atrophy
Tuberculous sialadenitis	Slow growing, non-tender localized swelling is commonly present. Pain, abscess, fistula, and nerve involvement are the late features
Tuberculous lymphadenitis (Scrofula)	Slowly enlarging cold abscess in the neck may rupture forming a sinus and an open wound
Lupus vulgaris	Single or several, unilateral, reddish-brown papules coalescing into erythematous plaques. Characteristic lesion is apple-jelly nodules

Table 3: Step by step approach to diagnose orofacial TB lesion

Medical history

Symptoms like cough of 3 or more weeks, chest pain, hemoptysis, low grade fever, night sweats, chills, loss of appetite and weight, mucoid sputum that changes to purulent are suggestive of TB.[62] Prior TB exposure or TB treatment or disease such as HIV infection that increase risk for TB should be enquired

Physical examination

Patient's general health is assessed and any abnormal local finding is observed

Screening tests: To determine if a person has been infected with TB bacteria: Latent TB infection (LTBI) or has progressed to active TB disease

Tuberculin skin test or Mantoux test

Is performed by injecting a small amount of PPD tuberculin into the skin of forearm. After 48 to 72 hours site of injection is checked for raised, hard area or swelling if present

TB blood tests or interferon-gamma release assays or IGRAs: Measure the ability of the *Mycobacterium tuberculosis* antigens to react with immune system. Two IGRAs that are approved by the U.S. Food and Drug Administration are:[63]

QuantiFERON®-TB Gold In-Tube test (QFT-GIT): Uses an ELISA format to detect the whole blood production of interferon γ with great sensitivity (89%)

T-SPOT.TB test: Measures T cells primed to *Mycobacterium tuberculosis* (MTB) antigens

Tuberculosis radiology

Pulmonary TB

Chest radiograph: In adolescents and adults upper lobe cavitary consolidation with occasional mediastinal or hilar lymph node enlargement or pleural effusion. In infancy and childhood, intra-thoracic lymph node are enlarged, pleural effusion is seen, and lung lesions are present in lower lobes[64]

Extrapulmonary TB

Computerized tomography (CT) scan, magnetic resonance imaging (MRI) scan, or ultrasound scan of the affected part of the body

Smear from 3 sputum samples obtained for acid-fast bacilli (in the absence of sputum sample, alternative sample sources are gastric washings, laryngeal swab, bronchoalveolar lavage, bronchial washings, fine-needle aspiration and tissue biopsy

Nucleic acid amplification testing (NAAT): Is a molecular technique used to directly detect the genetic material of the infecting organism or virus. NAAT may speed the diagnosis in smear-negative cases and may be helpful to differentiate non-tuberculous mycobacteria.[65] NAAT may utilize polymerase chain reaction (PCR) technique or transcription-mediated amplification (TMA) or other forms of nucleic acid amplification methods to detect mycobacterial nucleic acid. The two most common commercially available tests are the amplified *Mycobacterium tuberculosis* direct test (AMTD, Gen-Probe) and amplicor (Roche Diagnostics). The AMTD test appears to perform better than other currently available commercial tests.[66]

Sputum culture:

It confirms diagnosis of TB, is more sensitive than smear staining, and evaluates drug sensitivity. Traditionally, cultures have used the Löwenstein-Jensen (LJ), Kirchner, or Middlebrook media (7H9, 7H10, and 7H11). New automated systems that are faster include the MB/BacT, BACTEC 9000, VersaTREK, mycobacterial growth indicator tube (MGIT) and the microscopic observation drug susceptibility assay culture[67]

Blood Count

Lymphocytosis and raised erythrocyte sedimentation rate (ESR) is usually present

HIV Testing

TB patients should be tested for HIV within 2 months of diagnosis

Table 4: Recent anti-tuberculosis drugs in clinical trials

Class	Mechanism of Action	Name of drug	Clinical trial phase
Diarylquinoline	Inhibition of ATP synthesis and disruption of membrane potential	Bedaquiline	III
Nitroimidazoles	Inhibition of synthesis of mycolic acids; poisons the bacterial cell by releasing nitric oxide when metabolized	Delamanid	III
		PA-824,	II
		OPC-67683	II
		TBA354	Preclinical
Fluoroquinolone	Inhibition of DNA biosynthesis	Gatifloxacin, Moxifloxacin,	III
Ethylenediamine	Inhibition of cell wall biosynthesis	SQ109	II
Oxazolidinone	Inhibition of protein biosynthesis	AZD5847, Linezolid, Sutezolid, tedizolid (for MRSA)	II
Rifamycin	Blocks messenger RNA synthesis (transcription) by inhibiting the bacterial DNA-dependent RNA polymerase	Rifapentine	II/III

to delay in diagnosis and non compliance with the treatment. The main priority of the government should be prevention of development of drug resistance in TB and encourage research of new drugs to treat multidrug-resistant TB.

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