

Primary oral tuberculosis: A case series of a rare disease

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Abstract

Tuberculosis (TB) is still one of the most life-threatening infectious diseases, resulting in high mortality in adults and is commonly found in developing countries. Lung is primarily affected while extrapulmonary TB is rarely encountered. Oral lesions, although rare, can be seen in both primary and secondary stages of TB. Primary oral TB may present a diagnostic challenge as its clinical features can be nonspecific that mimics other diseases and is usually misdiagnosed. Thus, it is very important to be aware and be highly suspicious of oral TB especially in endemic area. We share 4 such cases of primary oral TB with uncommon presentations (two on the gingiva, one on the palate and one on the tongue) The diagnosis was made by histopathological examination, polymerase chain reaction analysis and Mantoux test. They were successfully treated with antituberculous treatment. In secondary TB, the oral manifestations may be accompanied by lesions in the lungs, lymph nodes or in any other part of the body and can be detected by a systemic examination.

Keywords: Gingiva, oral tuberculosis, palate, primary, tongue, tuberculosis

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Submitted: 01-Jun-2019, **Revised:** 04-Mar-2020, **Accepted:** 23-Mar-2020, **Published:** 09-Sep-2020

INTRODUCTION

Tuberculosis (TB) is still among the most life-threatening infectious diseases, resulting in high mortality in adults.^[1] It is a chronic infectious granulomatous disease caused by *Mycobacterium tuberculosis*, an acid-fast bacillus (AFB), and less frequently by ingesting un-pasteurized cow's milk that is infected by *Mycobacterium Bovis* or by other atypical mycobacteria.^[1] Both primary and secondary types of TB can cause lesions in the oral cavity (OC).^[2] In secondary TB, lesions of the OC may accompany lesions in the pharynx, lungs, lymph nodes or skin.^[2] Extrapulmonary TB accounts for 25% of the cases with 10%–35% detected in the head and neck region.^[3,4] Oral manifestation of TB may affect people of all ages, especially the elderly, and

is usually presented as an ulcer. It has been hypothesized that auto-inoculation may occur when the infected pulmonary mucus interacts with wounded, susceptible areas of the mucosa, eliciting the emergence of lesion.^[5] So far, cases of primary TB of the tongue are published as an anecdotal case reports because of extreme rarity.^[6] Tubercular foci in OC secondary to primary TB of the lung is again uncommon if not rare.^[7] The incidence of oral TB is only 0.1%–0.4%.^[8] TB of OC even as a secondary form is uncommon.^[7] When oral lesions of TB are the sole manifestations of the disease, the clinician may face a diagnostic challenge.

The World Health Organization (WHO) definition of the case of extrapulmonary TB (EPTB) is: “any

Access this article online

Quick Response Code:



Website:

www.jomfp.in

DOI:

10.4103/jomfp.JOMFP_174_19

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How to cite this article: Hamid R, Sharma P, Sheikh RA, Bhat M. Primary oral tuberculosis: A case series of a rare disease. J Oral Maxillofac Pathol 2020;24:332-8.

bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.” From this definition are excluded the cases with both pulmonary TB and EPTB, which are recommended to be classified as pulmonary TB cases.^[9,10] The lack of specific pathognomonic signs makes the diagnosis of EPTB to be often overlooked by the clinician.^[2,11] Orofacial TB is uncommon and presents at different sites such as the mandible (alveolar and basal bone), head, face and neck lymph nodes, tonsils, salivary glands, maxilla and maxillary antrum, hard palate and soft tissues such as soft palate, uvula, the gingiva, tongue, muscles of mastication and buccal mucosa.^[11,12] OC involvement is very rare and was reported a long time ago. Morgagni described first case of lingual TB in 1761.^[6] De Paoli reported the first case of parotid gland TB in 1893.^[13] The incidence of TB in underdeveloped countries is increasing, and this is thought to be because of associated poor hygiene conditions and the greater prevalence of AIDS.^[14] Here, we report four cases of primary oral TB (two on the gingiva, one on the palate and one on the tongue). Clinical features of cases are summarized in Table 1.

CASE REPORTS

Case 1

A 37-year-old female reported to the department of oral medicine and radiology with a chief complaint of nonpainful swelling of the upper anterior gingiva for the past 8 months. The gingiva increased gradually in size with time. The patient had a history of weakness over the past 3–4 months, loss of appetite and loss of weight of about 5 kg during the past 3 months. Her medical history revealed no systemic problems, no cough with expectoration, no known history of contact with a tuberculous patient and no history of dental trauma or any surgery in the affected area. On examination, she was of average built, pulse, temperature and respiration rates were normal. Extraoral examination revealed no cervical lymphadenopathy. Intraoral examination showed diffuse enlargement of labial maxillary gingiva (marginal and attached gingiva) and alveolar mucosa extending from tooth number 13–23. The gingiva was red, irregular, pebbled and granular in appearance with surface ulceration [Figure 1a]. On

palpation, the swelling was slightly tender, firm and had a tendency for bleeding on provocation. The rest of the OC was normal. Complete hemogram and IOPA radiograph of 11, 12, 21 and 22 were advised. Results were within normal limits, except for a marginal rise in leukocyte count and an elevated erythrocyte sedimentation rate (ESR). IOPA radiograph revealed interdental bone loss in relation to 11 and 21. The patient was then advised tuberculin test, chest X-ray and sputum culture. A tuberculin (Mantoux) test was positive, suggesting tubercular infection. Chest radiography (posteroanterior view) revealed no abnormalities [Figure 1b]. Culture of sputum was negative for *M. tuberculosis*. An incisional biopsy from the maxillary labial gingiva adjacent to the central incisors was performed. Histopathological examination revealed clusters of epithelioid cells, caseating necrosis and numerous Langhans-type giant cells surrounded by a chronic inflammatory type of infiltrate [Figure 1c and d]. In view of these findings, a working diagnosis of primary tuberculous gingival enlargement was made. The patient was later administered antitubercular regime, and within 2 months of therapy, the lesion healed spontaneously [Figure 1e]. No recurrence was observed even after 6 months of follow-up. During this period, the patient was instructed not to undergo any surgical procedure within the OC. Further, conservative periodontal therapy, which included scaling and root planning, was carried out with minimal trauma to gingival and after consulting the physician in-charge.

Case 2

A 45-year-old female presented with a chief complaint of painful ulcer on the palate for the last 1 year, which gradually increased to the present size. She had received antibiotics (amoxicillin plus clavulanate) prescribed by local practitioners, but there was no response. She did not have any systemic complaints such as cough, fever or weight loss and had no history of any allergy. There was no cervical lymphadenopathy or any other abnormal findings. Intraoral examination revealed gingival ulcerations involving marginal and attached gingiva in relation to 11–14 and mucosa of the anterior hard palate. The ulcer is indurated, irregular, having an undermined margin and a yellowish granular necrotic base [Figure 2a]. Owing to suspicion of a malignant lesion, an incisional biopsy

Table 1: Demographic and clinical characteristics

Case number	Age (year)	Gender	Presented as	Masquerading
Case 1	37	Female	Nonpainful swelling of the upper anterior gingiva	NUG
Case 2	45	Female	Painful ulcer on palate	NUG/NUP
Case 3	23	Female	Nonpainful swelling of the gingiva	Gingival overgrowth
Case 4	49	Male	Painful and non-healing ulcerated lesion of the tongue	Oral SCC

NUG: Necrotizing ulcerative gingivitis, NUP: Necrotizing ulcerative periodontitis, SCC: Squamous cell carcinoma

was undertaken from anterior mucosa of hard palate following the baseline investigations which were within normal limits. Histopathological examination (HPE) of the surgical specimen showed a conserved epithelium covering the subepithelial layers, with widespread caseating granulomas surrounded by lymphocytes, epithelial cells and Langhans-type giant cells [Figure 2b]. No neoplastic changes were observed. Ziehl–Neelsen staining was negative. With all these data, the diagnosis of oral TB was suggested and systemic analyses were performed to determine its primary or secondary origin. The Mantoux test showed a positive reaction. Chest X-ray did not show any lesion suggestive of pulmonary TB. Three sputum specimens were smear negative and culture negative. Although the first clinical impression raised suspicion of a malignant or traumatic process, these were both dismissed based on the pathology results. In fact, the presence of caseating granulomas surrounded by lymphocytes, epithelial cells and Langhans-type giant cells confirmed the diagnosis of TB. The patient was referred to the department of infectious

diseases for further management. Treatment was started with isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1500 mg/day) and ethambutol (900 mg/day) for 2 months and the patient was asked to continue with the first two drugs for the next 4 months. No pulmonary signs and symptoms were present. The oral lesions resolved within 4 weeks of treatment [Figure 2c]. The patient was followed for 9 months after the treatment with no recurrence of lesion.

Case 3

A 23-year-old girl reported to the department of oral medicine and radiology with progressive, nonpainful swelling of the gingiva on the labial aspect of the upper and lower anterior teeth with 6 months' duration. There was a history of evening rise in temperature and weakness over the last 3 months. The patient also had a loss of appetite over the last 4 months and a weight loss of about 4.5 kg during the last 8 months. There were no systemic problems, no cough with expectoration and no history of dental trauma or surgery in the affected area. Extraoral examination revealed no cervical lymphadenopathy. Intraoral examination revealed diffuse enlargement of the upper and lower gingiva on the labial surface of anterior maxillary and mandibular teeth [Figure 3a]. On palpation, the swelling was slightly tender and firm. The rest of the OC was normal except for the few deep carious teeth. Differential diagnoses were enlargement due to drugs, infection and hematologic malignancy. The possibility of drug-induced enlargement was ruled out based on medical history. The biochemical tests were within normal limits, except for a marginal rise in leukocyte count ($13 \times 10^9/L$) and an elevated ESR of 56 mm/h (Westergren method), which ruled out leukemia-associated enlargement and raised the possibility of one of the common causes of high ESR, TB. An incisional biopsy was carried out under LA in relation to the gingiva of the mandibular right central incisor, in collaboration with the department of periodontics and implantology. Histopathological examination was carried out that revealed clusters of epithelioid cells surrounded



Figure 1: (a) Red, irregular, pebbled and granular with surface ulceration (b) chest radiograph showing absence of foci of infection. (c) Photomicrograph showing granulomatous inflammation with Langhans-type giant cells and focal caseous necrosis in H&E (x20). (d) Photomicrograph showing Langhans-type giant cells in H&E stain (x40). (e) Healing lesion (2 months after start of ATT)

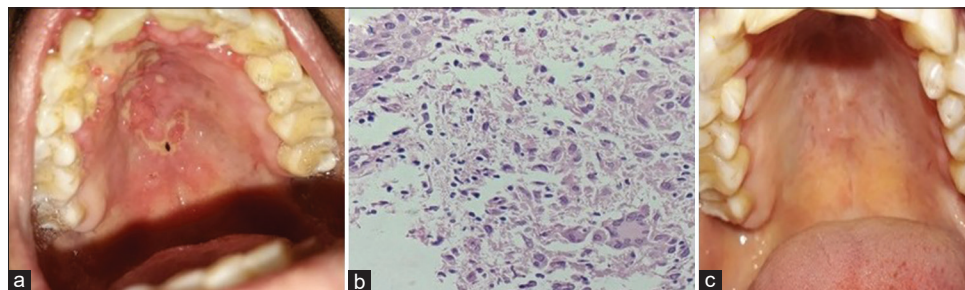


Figure 2: (a) Indurated irregular ulcer, having a yellowish granular necrotic base (b) histopathological slide showing giant cells (x40) (c) oral lesions resolved within 4 weeks of treatment

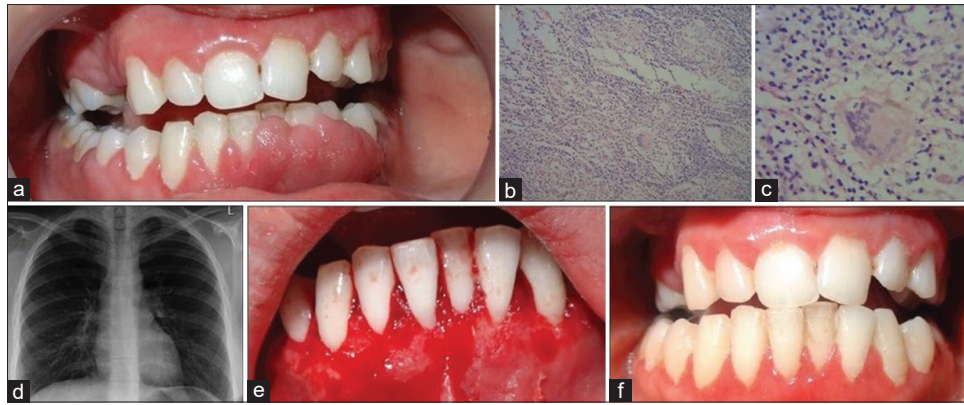


Figure 3: (a) Diffuse enlargement of both the arches and lobulated appearance of the mandibular labial gingiva extending up to the left first molar (b) microscopic picture reveals numerous non-caseating granulomas ($\times 10$) (c) histopathological picture of the lesion under $\times 40$ magnification reveals Langerhans giant cells and epithelioid cells (d) chest X-ray does not reveal any abnormality (e) immediate post-operative picture of the lesion (f) intraoral picture after 1-year follow-up does not reveal any recurrence of the lesion

by a chronic inflammatory type of infiltrate. There was no evidence of caseating necrosis, but numerous Langhans giant cells were visible in the clusters of epithelioid cells suggestive of a “hard tubercle” [Figure 3b and c]. To eliminate the possibility of localized granulomatous changes superimposed on an area of gingival enlargement, incisional biopsy was repeated in the remaining three quadrants. Histopathology showed similar granulomatous changes in all tissue specimens examined. The tuberculin (Mantoux) test was positive, suggesting tubercular infection. Chest radiography (posteroanterior view) revealed no abnormalities [Figure 3d]. A computed tomography scan of the head and neck region was also performed to determine the status of the underlying maxilla and mandible. The scan did not reveal any bone abnormalities. A culture of the sputum, obtained by forceful coughing, was negative for *M. tuberculosis*. Special staining of formalin-fixed, paraffin-embedded tissue specimens for Mycobacteria, i.e., Ziehl–Neelsen and auramine–rhodamine stain, was negative. An immunologic test to detect antibodies against Mycobacterium in the patient’s serum (ELISA) was positive. Polymerase chain reaction (PCR) assay was also carried out using six 5- μm sections of paraffin-embedded tissue to identify specific sequences of *M. tuberculosis* complex, with adequate controls. The DNA was used as an amplifying target for the sequence IS-6110, which is specific for *M. tuberculosis*. Positive PCR results confirmed the presence of *M. tuberculosis* in the tissue samples. In view of these findings, a final diagnosis of primary tuberculous gingival enlargement was made. In consultation with the patients’ physicians, antitubercular therapy (ATT) was initiated. During this period, the patient was instructed not to undergo any ultrasonic scaling and polishing or surgical procedure within the OC and was warned about the chance of transmitting the disease to others via aerosol

and salivary contamination. After completion of a 6-month regimen of basic periodontal therapy, which included scaling and root planning, oral hygiene instructions were instituted under CDC-issued guidelines. This resulted in significant regression of the enlarged gingivae in both the arches. Gingivectomy and gingivoplasty were performed to shape and contour the residual enlargement under universal aseptic conditions [Figure 3e]. No recurrence of lesion occurred during 1-year follow-up [Figure 3f].

Case 4

A 49-year-old male was referred to our department with the complaint of painful and non-healing ulcer of the tongue for 4 months. There was no history of fever, night sweats, cough, decreased appetite and weight loss. He did not give any history of traumatic episode preceding the development of tongue ulcer. He denied any history of similar lesions in the past. He is an occasional smoker. The rest of his medical and surgical history was unremarkable. His dental history was not significant. There was no history of TB in his family members. He was repeatedly treated in a government hospital with topical antiseptics and oral antibiotics (ampicillin plus cloxacillin and metronidazole) and analgesics, but the lesion did not subside so he was referred to our hospital for the further management. On general examination, he was of average built. Intraoral examination revealed an indurated ulcer measuring 1.5 cm \times 1.0 cm on the left dorsolateral border of anterior part of tongue. It was tender on palpation with irregular borders and did not bleed on touch. The remaining part of the tongue appeared normal in texture and color. Mobility of the tongue was normal. He had poor oral hygiene along with sharp tooth in relation to 34. There were no palpable cervical lymph nodes. Provisional diagnosis of chronic traumatic ulcer was made as the possibility of ulcer due to repeated trauma by the sharp tooth. Chest

X-ray did not reveal any evidence of active lesion. Sputum for AFB was negative on Ziehl–Neelsen stain. Complete blood count was within normal limit. His ESR value was 20 mm/hr. Serum biochemistry and renal function tests were within normal limits. Serological investigation for human immune deficiency virus (HIV) was negative. Coronoplasty of adjacent sharp cusps was done, and since the ulcer presented for more than 2 months, an incisional biopsy was taken under local anesthesia containing an ulcerated lesion along with the normal looking margin and the specimen was sent for HPE. Microscopically, the lesion revealed the stratified squamous epithelium with granulomatous inflammation containing Langhans-type giant cells, epithelioid cells and foci of caseous necrosis, strongly suggestive of TB. The patient was then started on ATT. The ulcer gradually started fading once drug therapy was started (ATT) and the tuberculous ulcer healed completely by the 2 months of ATT containing isoniazid, rifampicin, pyrazinamide and ethambutol. The patient was advised to continue ATT containing isoniazid and rifampicin for another 4 months. At the end of total 6 month's ATT course, there was no evidence of ulcer at the primary site.

DISCUSSION

Primary TB (TB) of the OC, including tongue, is very rare because of continuous cleaning of oral mucosa by saliva and paucity of lymphoid follicles in tongue.^[15-17] Secondary TB of OC is 0.2%–1.5% of extrapulmonary TB cases.^[18,19] The WHO estimates that 2 billion people or one-third of the world's population are infected with tuberculous bacilli and the global TB incidence is growing at 1% a year.^[15] Despite these staggering figures, TB of the OC is rare.^[15-17] Furthermore, most cases of oral TB are mainly secondary to pulmonary TB and rarely primary in origin.^[15] Such lesions are suspected to be caused by implantation of infected sputum into a break in the mucosal surface during coughing episodes. Transmission during dental practice has also been described.^[15] Clinical manifestations of oral TB are varied and usually manifests as nonhealing ulcer but can also appear as nodules, swelling, fissures and as osteomyelitis of jaw bones. Oral TB ulcers are usually single rather than multiple; they have an indurated, irregular and undermined margin with a necrotic base. The ulcer may be initially painless but may become painful with the passage of time.^[20] Other manifestations of oral TB may include nodular lesion or cold abscess.^[6,19] Three forms of oral TB have been described: acute miliary, chronic ulcerative and lupus vulgaris.^[21] Overwhelming majority (about 93%) of the oral lesions are ulcers and approximately half

of which affect the tongue.^[22] Three of the cases in our series were chronic ulcers and one presented as gingival overgrowth. The ulcers were on the lateral margin of tongue, anterior gingiva and anterior palate. Primary TB of the OC is extremely rare and the published literature is only in the form of case reports.^[6,23,24] There appears to be a geographical variation regarding which age group is affected by primary TB. In Western literature, it is mentioned that primarily oral TB affects children and adolescents and is often associated with enlarged cervical lymph nodes.^[25] A few case reports from India also fall into younger age group.^[6,24] In this series, the mean age of the patients was 38.5 years, while youngest being 23-year-old female. TB of OC can be seen in adults, but primary TB of lip and uvula among pediatric age group has been reported occasionally.^[24] Wang *et al.*^[26] reported a series of 20 cases from Taiwan, wherein 55% of the patients were older than 50 years and the most common location was buccal mucosa and/or vestibule (5 cases), followed by the alveolar mucosa (4), palate (2), lip (2) and tongue (1 case). Rarely, direct inoculation may result in primary oral TB. The site most commonly affected is the gingiva where primary TB appears as a diffuse erythematous patch or as diffuse gingival enlargement.^[27] Primary TB of the OC has been reported in HIV infected immune deficient cases as an indicator of HIV infection; however, most of the published literature pertains to cases with intact immune status similar to the cases under discussion.^[23,28] Other TB lesions, diffuse glossitis or fissures, have also been reported, but they are exceedingly rare.^[29] Although the dorsal surface is more commonly involved, involvement of the ventral surface has also been described.^[29]

The tuberculin sensitivity assay, also called Mantoux test, is the standard procedure to diagnose TB. The assay includes the intradermal inoculation of a purified protein derivative of *M. tuberculosis* to assess the cellular immune response to the antigens. An inflammatory reaction takes place in *M. tuberculosis* sensitized patients. Inspection is conducted after 2–3 days and is valid for 7 days. The evaluation is based on the diameter of the inflammation area measured transversally against the longitudinal direction of the challenged forearm. An inflammation area over 10 mm in immunocompetent subjects is considered a positive result. In immunocompromised patients, an area larger than 5 mm indicates TB. In turn, the minimum size of inflammatory area in low-risk individuals and children under 15 years of age is 15 mm. Although the Mantoux reaction is the method of choice in TB diagnosis, the test has a few limitations, such as the low sensitivity in immunocompromised patients (which points to the risk of false negative results), the difficulty to use in children,

the subjective character of interpretations and the need for a second appointment for confirmation purposes in some cases.^[30] The oral manifestation of TB may present as an ulcerative, painless lesion on the palate, lips or tongue, accompanied by persistent cervical lymphadenopathy.^[29] Our first case showed non painful ulcer on gingiva, second one had painful ulcer on palate, third case had non painful gingival swelling and the fourth one had painful ulcer on tongue. The male:female ratio in our series was 1:3. The differential diagnosis of TB ulcers includes a variety of ulcerative diseases and conditions, such as squamous cell carcinoma, traumatic ulcers, aphthous stomatitis, syphilitic ulcers, actinomycosis, Wegener's granulomatosis, sarcoidosis, leishmaniasis, zygomycosis and Hansen's disease.^[31] It is important to highlight that oral ulcers may present a similar picture,^[32] requiring a diagnosis based on microscopic findings in addition to the Mantoux test and bacilloscopy.^[33] In our cases, aphthous ulcer was excluded by the absence of initial multiple painful lesions and there was no history of recurrent ulcers. Syphilitic ulcer was ruled out by serology and silver staining done on tissue section. HIV was ruled out by serology. Sarcoidosis was ruled out by the absence of lung involvement on radiological examination and presence of caseation and AFB on HPE. Diagnosis of oral TB was based on HPE, PCR analysis and Mantoux test.^[34,35] Due to selective scarcity of bacilli within tissue, mycobacteria can be demonstrated only in 27%–60% of cases. Culture of mycobacteria had good result, but it lacks sensitivity and takes 4–6 weeks.^[34,36] Chest X-ray is done to exclude the possibility of pulmonary TB. Oral ulcers may be indurated and is often painful (pain on deglutition, burning sensation and otalgia). The gingival involvement is the second form of oral TB after tongue TB.^[25,37] For ulcers of the tongue, deeper biopsies are mandatory. Biopsies as superficial may not find the histopathological lesion due to epithelial hyperplasia.^[38] PCR assays as development of DNA probes may use as more sensitive and rapid diagnosis tests, but are more expensive. The risk for TB is greater in patients with HIV infection than in non-HIV.^[39] Our patients were HIV negative. During the treatment of tuberculous pulmonary lesions, remission of tuberculous ulceration of the tongue can appear together with remission of lung TB lesions.^[39] Lingual TB does not need surgical resection and prognosis is favorable after antituberculous treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will

not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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