Case Report

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Primary Oral Tuberculosis Imitating Malignancy- A Rare Case Report

Dentistry Section

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ABSTRACT

Tuberculosis is caused by *Mycobacterium tuberculosis* and is an ancient disease causing major morbidity and mortality worldwide. Though tuberculosis affects lungs in the majority of the cases but can affect other organs including the oral cavity as a primary site. Oral lesions can be seen in both primary and secondary forms of tuberculosis. The present article reports a case of a primary oral tubercular ulcer of buccal mucosa in a 36-year-old female, which based on clinical features was provisionally diagnosed as squamous cell carcinoma. The diagnosis of oral tuberculosis was confirmed by histopathology, blood and immunological investigations. The patient then was kept on Antitubercular Therapy (ATT) and the lesion showed healing markedly. Thus, oral tubercular lesions are rare and are difficult to diagnose, so every chronic, abnormal looking lesion should be examined cautiously for early diagnosis and prompt treatment.

Keywords: Granuloma, Grocott's silver stains, Mycobacterium tuberculosis, Oral ulcer

CASE REPORT

A 36-year-old female visited the Dental Outpatient Department (OPD) with a chief complaint of pain and non healing ulcer in the lower left back tooth region for 30 days. Initially, the ulcer was painless but became sore after two weeks. She had taken a course of antibiotics but there was no relief. No history of fever, weight loss, cough and expectoration reported. There was no relevant medical or any other dental history.

Intraoral examination revealed a single ulcer in the buccal vestibule in relation to 36, 37 and 38 region, extending from the mesial surface of 36 to the distal surface of 38, measuring 2.5×3 cm, with a shallow ulcerated base and ill-defined margins. The ulcer had white edges and indurated borders covered with whitish-yellow exudate. Her left submandibular lymph node was found to be palpable and firm in consistency, but was non tender and was not fixed to the underlying tissues [Table/Fig-1].

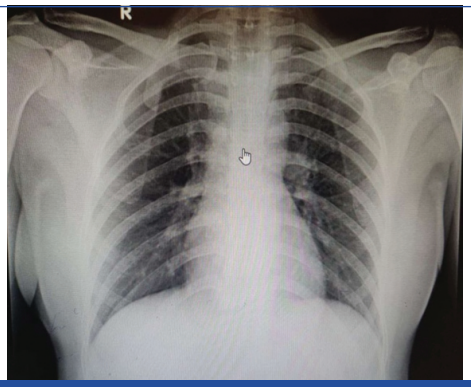
Based on the clinical examination, a provisional diagnosis of squamous cell carcinoma or any other malignancy was made and an incisional biopsy was advised. The patient had refused for incisional biopsy and was lost to follow-up. She returned after two weeks with a history of extraction of 38 from a private dental practitioner and persisted with the lesion.

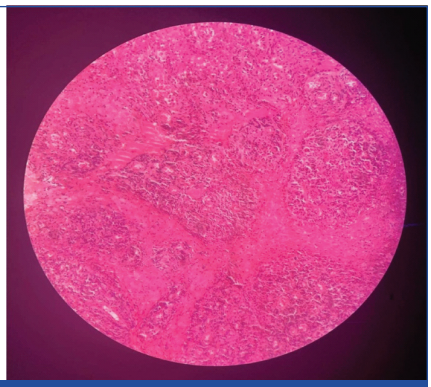
As part of the investigations, the patient was advised for a chest radiograph and no remarkable changes were seen [Table/Fig-2]. Haematological investigations revealed all parameters within the normal range except for a low Haemoglobin level (7.9 gm%) and raised erythrocyte sedimentation rate (90 mm/hour).

Later incisional biopsy was taken and on microscopic examination of the Haematoxylin and Eosin (H&E) stained tissue section revealed fibrous connective tissue stroma exhibiting very dense inflammatory cell infiltrate, numerous blood vessels with granuloma formation which was predominantly composed of epitheloid cells, Langhan's giant cells and lymphocytes [Table/Fig-3,4].

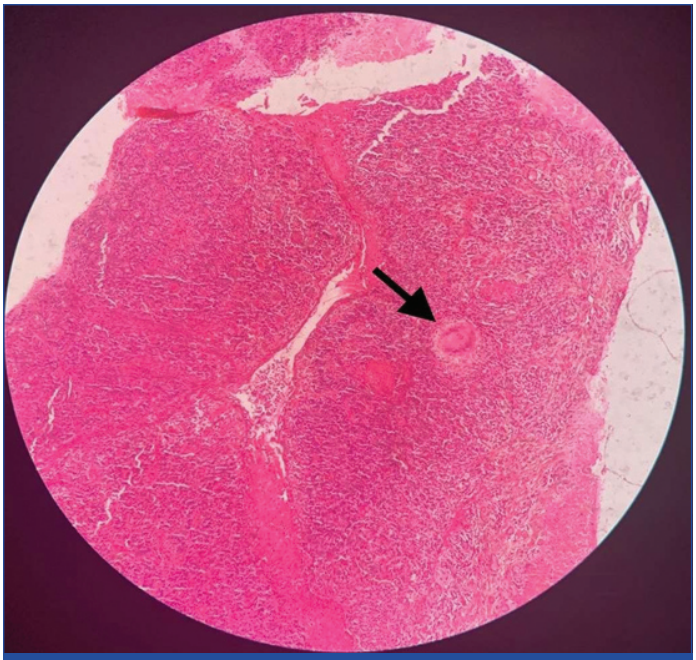
The overlying stratified squamous epithelium was proliferative. But there was no feature of malignancy seen in the tissue. Based on the histopathological findings, it was believed to consider granulomatous infections in the differential diagnosis of the lesion. Therefore, the sections were subjected to special staining. To rule out fungal infections Periodic-acid Schiff (PAS) and Grocott's Silver stains were done which turned out to be negative. Similarly Gram stain to rule out bacterial infections was also negative. Also, the Ziehl-Neelsen stain did not give a positive result. But still, the possibility of Tuberculosis was not ruled out.

Due to the non availability of Polymerase Chain Reaction (PCR) at the tertiary care centre, the patient was advised for QuantiFERON-TB Gold (an interferon-gamma (IFN- γ) release assay) test that aids in the detection of *Mycobacterium (M) tuberculosis*. This test is considered to be a good alternative to the Tuberculin skin test The test confirmed the presence of antibodies against mycobacterium tuberculosis. For further opinion and treatment the patient was asked to consult the physician, where she was initiated with World





[Table/Fig-1]: Intraoral photograph showing an ulcer on the left buccal mucosa covered by a yellowish pseudomembrane. **[Table/Fig-2]:** Chest radiograph showing no remarkable changes. **[Table/Fig-3]:** Photomicrograph showing granulomatous inflammation (H&E stain 20X). (Images from left to right)



[Table/Fig-4]: Photomicrograph showing Langhans giant cells with multiple nuclei. The nuclei can be seen organised in a horse-shoe shaped pattern at the periphery (Black arrow) (H&E stain 20X).

Heath Organisation (WHO) recommended category 1 Anti-tubercular Therapy (ATT) Directly Observed Treatment, Short Course (DOTS). Her condition started improving dramatically after a few days and after six months of ATT, the oral condition improved markedly [Table/Fig-5].

[Table/Fig-5]: Intraoral photograph showing complete healing after six months.

DISCUSSION

Tuberculosis caused by Mycobacterium tuberculosis is an ancient disease existing in society for thousands of years but still has much to explore [1]. Though the cases have shown a declining trend in recent years it remains a major health problem [2]. Looking at the global picture approximately 10 million people have suffered from tuberculosis in 2019 [1]. And Indian picture is even more fearsome with 2.8 million cases yearly thus making the maximum incidence of Tuberculosis (TB) in the world. Over 435,000 Indian lives are claimed by TB every year which puts tuberculosis in the list of top ten etiologies of casualities occurring in our nation [3,4]. Though it is progressing towards better but it is going very slowly. As per anticipation it will not be possible for the world to end TB by 2035 as it has been visualised in the End TB Strategy [5].

Its prevalence ranges from 0.5-1% of all cases of tuberculosis [6]. Though tuberculosis affects the lungs in a majority of the cases but can affect other organs including the brain, kidney, spine and oral cavity. Oral TB is considered a rare disease [7]. To the best of authors knowledge, primary oral TB is a very rare entity and the number of cases reported in literature is very less so far [4,5].

Oral lesions are rare. Few characteristic features that are responsible for less number of cases seen include an intact oral epithelium, less number of lymphoid follicles and a regular cleansing of oral mucosa by saliva [8]. It has been believed that a breach in the continuity of the oral epithelium results in the primary inoculation by the bacilli present in the sputum [9].

Chronic irritation or inflammation might favour the localisation of the organism and a small tear facilitates the entry into mucosa [10]. Poor oral hygiene, trauma, dental extraction, cysts, abscesses, leukoplakia, periapical granulomas periodontitis are the local predisposing factors [11,12]. In the present case, the poor oral hygiene could have been one possible reason for the bacterial spread as there was gingivitis and periodontitis seen.

Though oral TB lesions can be primary or secondary in occurrence majority of them encountered in the mouth are secondary to infections of lungs [13]. Primary lesions are not common and are usually seen in younger patients whereas secondary lesions are common and are seen in association with pulmonary disease in middle-aged and elderly patients [14]. Contrary to this, the indexed case report case presented as a primary lesion in a middle-aged female.

Oral TB though can affect any part of the oral cavity, the most commonly affected site include tongue, palate, palatine tonsil, lips, buccal mucosa, gingiva, floor of the mouth and salivary glands. Out of these sites tongue is the most common site of involvement [13]. It has also been described in the literature that dental practice can also transmit the infection [14]. Therefore, clinicians should be aware and should look for the symptoms associated with primary TB which is the active source of secondary TB so that the disease can be diagnosed early and prompt treatment can prevent further debilitation [14,15].

Three forms of oral TB have been described namely acute miliary, chronic ulcerative and lupus vulgaris [16]. Out of all the three forms of TB, most of the lesions present themselves as ulcerations and are seen most commonly (about 93%) on the tongue. [17-20]. This case also presented as a chronic non healing ulcer but on buccal mucosa.

The important feature of tubercular ulcer is that it is often single [21]. Margins of the lesion are irregular, indurated, undermined and ragged. The floor of the ulcer can be shielded with yellowish exudate or bluish granules, which was similar to this case [22,23].

Clinicians should be cautious about the chronic non healing ulcers in the oral cavity and should consider TB in the differential diagnosis as at times syphilitic ulcers, malignant ulcers and other granulomatous ulcers may have similar presentation [Table/Fig-6]. Nanda KD et al., Von Arx DP and Ram H and Kumar S, have also reported such occurrences in the past and their findings are consistent with the present case [14,19,23].

It becomes imperative for the practitioner to completely examine the patient including signs and symptoms of pulmonary TB with various available diagnostic tests inclusive of clinical, radiological, bacteriological and serological examination. This should be followed by a biopsy for histopathological examination and PCR analysis that can further help in the final diagnosis [17].

Disease	Number of ulcers	Associated soreness	Course and duration of the disease	Presentation	Clinical and diagnostic approach
Oral tuberculosis	Single	Not in primary TB but present in secondary TB	Persistent ulcer lasting for more than three weeks, general symptoms like fever, cough, weight loss might accompany	Ragged, indurated, ragged margins, yellowish exudate, trelat granules, cobblestone appearance	Tuberculin skin test - Heaf test, Mantoux test. Radiology- Chest X-ray, cavitation is the hallmark of postprimary TB, chest computed tomography showing tree-in-bud pattern Acid-fast bacilli smear microscopy and culture-e, Ziehl-Neelsen microscopy, fluorescence and light emitting diode microscopy, quantiferon TB Gold, T-spot, culturing on solid media (Lowenstein, Stonebrink or Ogawa medium). Molecular methods- Nucleic acid amplification testing, line probe assay, Xpert MTB/RIF, polymerase chain reaction. Histopathology- granuloma formation composed of epitheloid cells, langhan's giant cells and lymphocytes.
Oral squamous cell carcinoma	Single	No initial soreness but can become painful in the course of time	Persistent ulcer which might last longer	Irregular, ragged margins, indurated base, verrucous or cauliflower like growth might accompany	Tentative diagnosis of squamous cell carcinoma is based on its patient history, clinical presentation, its location and its morphological appearance doctor's interpretation of clinical information, appearance, morphology, location and patient reported history. Histopathology is the gold standard for diagnosis of squamous cell carcinoma, but a few non invasive optical technologies like dermascopy and RCM may enhance clinical diagnosis accuracy.
Recurrent aphthous ulcer	Single/ Multiple	Yes	Recurrent ulcers at different sites and spontaneously heal in 10-15 days	Shallow ulcer, red halo	Diagnosis of RAS is given on the basis of patient history and clinical appearance based on the clinical history and a physical examination. The additional tests include: Blood tests: complete blood count, iron, ferritin, folic acid, zinc, magnesium, and vitamins (B1, B2, B6 and B12). Microbiological tests: Tzanck smear test or polymerase chain reaction for herpes virus and culture of fungi and bacteria. Punch or incisional biopsy.
Syphilis	Single	No	Ulcer may last for 2-6 weeks with spontaneous healing	Smooth, indurated margins	Wassermann test and Hinton test (based on flocculation). Examining the exudates of the active lesion under a dark field microscope for spirochaetes. Characteristic pathology involves granulomas with epithelioid histiocytes, few multinucleated giant cells and occasional necrosis.
Lichen planus	Single/ Multiple	Yes	Recurrent ulcers preceded by subepithelial bullas	Shallow vast ulcer, wickham's striae present	The characteristic clinical features are sufficient to make a correct diagnosis if characteristic lesions are present. Oral biopsy with histopathologic interpretation is recommended to confirm clinical diagnosis and also to exclude dysplasia and malignancy. The value of direct immunofluorescence for confirmation of disease is well accepted.
Pemphigoid	Single/ Multiple	Yes	Recurrent ulcers preceded by subepithelial bullas	Moderate shallow ulcer, non indurated margins	The characteristic clinical features and a subepithelial vesicle or bullae on routine histologic analysis is the key to diagnosis. The diagnosis is also based on direct and indirect immunofluorescence studies.
Sarcoidoisis	Single/ Multiple	Yes		Papules or submucosal nodules with occasional ulcerations	The gold standard to diagnose sarcoidosis is microscopic examination. The presence of non necrotising granulomas supports the diagnosis. The Kveim-siltzbach test may also be an important aid in the early and accurate diagnosis of the disease.
Chrohn's disease	Single/ Multiple	Yes	Recurrent ulcers	Cobblestone appearance, deep linear ulcerations, mucosal tags	Diagnosis and management of crohn's disease is based on clinical signs and symptoms combined with laboratory tests, endoscopy and imaging techniques. Endoscopy stands as the gold standard for the evaluation of patients with crohn's disease.
Leukaemia	Single/ Multiple	Yes	Short duration	Ulceration with necrotic slough and erythematous periphery	Complete blood count can be helpful for dentists in cases suggestive of leukaemia, but a bone marrow biopsy and immunophenotyping of peripheral blood are necessary for a final diagnosis.
Histoplasmosis	Single/ Multiple	Yes	Persistent ulcer for more than three weeks. General symptoms like cough, pulmonary changes might appear	Irregular and indurated margins	Histologic findings of histoplasmosis typically show diffuse lymphohistiocytic infiltrates with fungal elements about 2-4 µm in size detected within the cytoplasm of histiocytes. Well formed granulomas are generally rare. Special stains, such as GMS and periodic-acid schiff methods will highlight the fungal organisms' cell wall. A classic halo appearance caused by the cytoplasm retracting from the thick cell wall is helpful in identifying the fungi.

[Table/Fig-6]: Differential diagnosis of oral tuberculosis [15].
TB: Tuberculosis, RCM: Reflectance confocal microscopy, T-Spot test: Tuberculosis-specific enzyme-linked immunospot assay, Xpert MTB/RIF: Mycobacterium tuberculosis complex (MTBC) and resistance to rifampin (RIF), RAS: Recurrent aphthous stomatitis; GMS: Grocott-Gomori's methenamine silver stain

Special stains play an important role in diagnosing bacterial infections [24]. But in this case, Ziehl Neelsen stain was negative and it still did not rule out TB as many studies have reported that very small percentage of biopsy specimens or cytosmears impart positive staining for acid-fast bacilli due to the paucity of organisms in sputum [25]. In this case, PCR could not be performed due to non availability at the tertiary centre. Clinical history, radiological examination and immunological tests helped in making the final diagnosis. There was no history of trauma which ruled out any traumatic or aphthous ulcer, further the squamous cell carcinoma was also ruled out due to no evidence of carcinomatous changes on histopathological examination. Raised ESR and positive TB Gold test helped in diagnosing the lesion.

CONCLUSION(S)

Oral tubercular lesions are rare and are difficult to diagnose, so every chronic, abnormal looking lesion should be examined cautiously for early diagnosis and prompt treatment. Diagnosing the disease early can reduce the mortality and morbidity of the patients.

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