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OTHER ARTICLES

Submandibular Gland Tuberculosis: A Literature Review and Update

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Abstract Submandibular salivary gland is an uncommon and unusual site for tuberculosis. It is a rare extrapulmonary manifestation of a common infection caused by Mycobacterium tubercle bacillus. Submandibular gland TB can be due to primary or secondary infection. The clinical features are non-specific and depend on its manifestations. A delay in diagnosis is common because of the rarity of disease. Direct histological examination is the best method of diagnosis. As the disease is curable with antituberculous drugs; treatment should not be withheld in suspected cases until the diagnosis is confirmed. Surgery is indicated for non-responsive disease and complications. Till date, only 15 cases have been reported in the literature. First case was reported in the year 1990. The authors encountered three cases in last 10 years. The aims of this study are to review clinical presentation, epidemiological features, diagnostic methods and to provide our data and guidelines for optimum management of this rare pathology.

Keywords Submandibular gland · Tuberculosis · Rare disease · Difficult diagnosis · Curable with drugs

Introduction

Tuberculosis of major salivary glands is rare and involvement of submandibular salivary gland with tuberculous infection is even rarer. Submandibular salivary gland TB has non-specific clinical features, characteristic epidemiological features, and a very effective medical treatment. It is difficult to diagnose this pathology. In patients with a high index of suspicion for the tuberculous etiology, treatment should not be withheld until the diagnosis is confirmed. Most of our knowledge about this rare disease is based on a few case reports and small case series. Till date, only 15 cases have been reported in the literature. First case was reported in the year 1990 [1]. The authors encountered three cases in last 10 years. The aims of this study are to review clinical presentation, epidemiological features, diagnostic methods and to provide our data and guidelines for optimum management of this rare pathology.

Methods

Electronic searches were undertaken in PUBMED and MEDLINE using the MeSH terms "submandibular gland" in combination with "tuberculosis", "tuberculous", "tubercular", "miliary tuberculosis", "disseminated tuberculosis", "tuberculosis in immunocompromised patients". A total of 15 cases have been identified in various case reports and case series. All resulting titles, abstract, and full text, whenever available, were read and kept for reference, and the findings were summarized.

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Epidemiology

With 20% cases, India accounts for the highest TB burden in the world [2]. Extrapulmonary TB (EPTB) accounts for one-third of TB cases in India [3, 4]. Tuberculous lymphadenitis is the most common form of extrapulmonary tuberculosis; cervical lymph nodes are the most commonly affected group of lymph nodes [4]. Involvement of head and neck region with TB is common; accounts for 10% of EPTB cases [5] but salivary glands rarely gets involved. Parotid gland TB is more common than other salivary glands [6]. The parotid gland gets more commonly involved in primary TB while submandibular gland involvement is more common with systemic TB [6]. The reasons for such kind of involvement are discussed in the next section. It has been observed that salivary gland TB including submandibular gland is more frequently encountered in Asian countries [6].

Submandibular gland TB has been found to be more common in males as compared to females. The median age of presentation is 33.5 years. The youngest reported case is 15 years of age [7] while the oldest patient is 45 years old [8].

Etiopathogenesis

Salivary glands including submandibular glands are relatively resistant to tuberculous bacillus. The following factors provide this immunity to gland:

1. Enzymatic action of saliva: In the submandibular gland, salivary enzymes act as a primary barrier and also a filter for the clearance of pathogens from the duct, vascular and local sources. The presence of fats and waxes in high percentage in the envelope of tubercle bacillus makes it highly resistant; once this envelope is gone, tubercle bacilli becomes susceptible [9]. Saliva contains thiocyanate ions and proteolytic enzymes which impart antibacterial property and enzymes result in complete bacteriolysis of tubercular bacillus [4, 6, 10].
2. Anatomical factor and physiological factor: continuous flow of saliva prevents lodging of Mycobacteria in the gland. Relative better flow of saliva in submandibular gland as compared to parotid gland makes submandibular gland a less common site for development of TB [4, 10, 11].

Patients with some risk factors, comorbid conditions and pathologies resulting in abnormal host-defence mechanism such as acquired immunodeficiency syndrome (AIDS) [6, 8] complement deficiency, leukemia are more prone to develop submandibular gland tuberculosis (TB) [6, 8]. The immunodeficiency virus (HIV), immunosuppressive medications including chemotherapeutic agents, use of steroid therapy, diabetes mellitus, are associated with an increasing incidence of submandibular gland tuberculosis [6, 8]. Development of pyogenic abscess as well as tuberculous abscess is more common with immunosuppressed states [6]. Other predisposing factors include nutritional deficiencies, chronic illness associated with bacterial infections, Wharton's duct obstruction, sialolithiasis, poor oral hygiene, dental infection and trauma to the gland or Wharton,s duct [8, 12].

The possible routes of tuberculous infection of submandibular gland are [4]:

(1) Haematogenous spread from a distant focus such as pulmonary TB is a rare cause of submandibular gland TB but this mode of transmission is more common than parotid gland TB.
(2) Lymphatic dissemination is considered as most common route of spread as lymphatic drainage from the oral cavity occurs mainly to the submandibular lymph nodes.
(3) Direct spread through tuberculous lesions in contiguous structure such as oral cavity lesions. The opening of Wharton's duct is present in the dependent part of the oral cavity; this anatomical factor predisposes submandibular gland to direct spread of bacillus from dental lesions as well as oral cavity lesions.
(4) Superinfection of a malignant lesion can occur; though no such case has been reported in the literature.
(5) Reactivation of a dormant bacillus in an immunosuppressed patient.

Submandibular gland TB can be due to primary or secondary infection [4]. In primary cases, there is no evidence of TB elsewhere. Primary and isolated submandibular gland tuberculosis is a rare occurrence. It is usually secondary to oral cavity or lymph nodal tuberculous infection or less commonly due to pulmonary infection [12].

Based on the mode of involvement, submandibular gland TB can be classified into the following types:

(1) Local, with isolated involvement of submandibular gland in the form of primary complex with caseation of the associated submandibular lymph nodes. Dissemination of infection from draining lymph nodes is the most common mode of involvement in patients with AIDS.
(2) Submandibular gland TB developing secondary to pulmonary TB.

(3) As a part of multifocal involvement of oral cavity and neck.
(4) Miliary TB, as a part of generalized TB resulting in involvement of submandibular gland as well. This is associated with immunosuppressed states.

Clinical Features

The clinical features of submandibular gland TB are non-specific and depend on its manifestations. The various manifestations of submandibular gland TB are [8, 13]:

1. Acute: an acute inflammatory lesion such as suppurative sialadenitis is rare.
2. Subacute: this is the most common type of manifestation. Majority of patients present in this form.
3. Chronic: chronic aymptomatic masses tend to grow slowly over years and often get confused with a benign neoplasm.

The most common presenting symptom is a slowly growing painless mass. Patients may also present with mild pain over the swelling. Acute presentation is rare, wherein the patient presents with a swelling below the angle of mandible associated with severe pain. Associated pain is often attributed to dental infection [8]. Tauro et al. reported a case in which patient presented with swelling and pain at the angle of mandible for which the patient sought dental opinion received antibiotics and analgesics; but his symptoms did not improve and then after a thorough work up, he was diagnosed to have acute suppurative tuberculous lymphadenitis [8]. Constitutional symptoms of TB such as evening rise of temperature, night sweats, weakness, anorexia and weight loss are rarely seen [8]. It is also important to look for features of active pulmonary TB and a past history of TB or TB contact. The disease is usually unilateral; only one case of bilateral submandibular gland TB has been reported [1].

Examination reveals firm, non-tender, fixed swelling in submandibular region with normal overlying skin. Cervical lymph nodes may be palpable. Oral cavity should be also be examined carefully to look for any caries teeth also look for any purulent discharge coming from Wharton's duct. The clinical features of three of our cases are given in Table 1.

Pathology

Generally, submandibular gland tuberculous lesions are solitary. Nodular lesions are small while abscesses may be large and multiple. Miliary lesions are multiple.

Macroscopy

The affected part of submandibular gland is mild to moderately enlarged in most cases. Diffuse massive enlargement of the gland is rare. The most common gross pathological finding is presence of multiple white caseating nodules in the gland, coalescing to form a large yellowish mass of solid consistency. Generally, submandibular gland tuberculous lesions are solitary. Nodular lesions are small while abscesses may be large and multiple. Miliary lesions are multiple. Like parotid tuberculosis, there are two pathological forms of submandibular gland TB-

1. Nodular or circumscribed form: In this form, there is an involvement of intraglandular or periglandular lymph nodes; it may take the form of a cystic lesion or cold abscess [4, 6].
2. Diffuse form: This is less common form. It consists of small and large areas of caseation or abscesses involving the entire gland parenchyma [4, 6].

Microscopy

Histologically, the hallmark of tuberculous lesions caused by Mycobacterium tuberculous bacillus are epitheloid granulomas composed of aggregates of macrophages (circumscribed by a cuff of T- and B- lymphocytes), epitheloid cells and langhans giant cells with variable degree of central caseous necrosis with presence of tubercle bacilli [6]. The lesions vary in size from 1 mm to > 1 cm. Fibrosis may develop in relation to epitheloid granulomas. Submandibular lymph nodes may show caseating granulomas.

Diagnosis

A delay in diagnosis is common because of the rarity of disease, clinical presentation is non-specific. Up to two-third of patients suffer delayed evaluation and management. Diagnosis is often made after major surgical resection on histopathological examination [4, 7]. Clinical presentation, epidemiological features, and imaging studies support the diagnosis of pancreatic TB but the definitive diagnosis requires demonstration of MTB on histopathologic examination [4]. Isolated submandibular gland TB is even rarer and diagnosis is challenging.

Table 1 Data of three cases of submandibular gland tuberculosis

Case	Age/sex	Clinical presentation/duration of symptoms	History of TB/ TB contact	Associated comorbidity	HIV status	Imaging study	PCR/culture	FNAC/ biopsy	Follow up and prognosis
1	39/M	Painful swelling, fever, anorexia, weight loss- 2 months	Yes	No	Positive	CXR, USG neck and CECT head and neck done	PCR positive, culture negative	FNAC positive	Received ATT for 12 months, recovered, alive
2	46/M	Painless swelling, fever, anorexia- 8 months	No	No	Positive	CXR, USG neck and CECT head and neck done	Culture and PCR positive	FNAC positive	Received ATT for 12 months, recovered, alive
3	45/F	Painless swelling, anorexia- 1 year	No	Hypothyroidism	Negative	CXR, USG neck and CECT head and neck done	Culture and PCR negative	FNAC negative, excisional biopsy positive	Received ATT for 9 months, recovered, alive

TB tuberculosis; *ATT* antituberculous treatment; *CXR* chest X-ray; *USG* ultrasonography; *CECT* contrast enhanced computed tomography; *PCR* polymerase chain reaction; *FNAC* fine needle aspiration cytology

Laboratory Evaluation

A number of laboratory abnormalities such as decreased haemoglobin level, mildly raised total leucocyte count, raised erythrocyte sedimentation rate, positive montoux test may be seen in a submandibular gland TB patient and help in supporting the diagnosis. However, there is no specific laboratory test to diagnose this pathology. HIV testing should always be done in all the patients suspected to have EPTB.

Role of Imaging Studies

Imaging studies have a limited role in correctly diagnosing submandibular gland TB and play only a supportive role. X-ray chest should always be done as it may show an active or old focus in the lungs. Ultrasonography (USG) is the initial study of choice for neck masses including submandibular gland lesions. It is important in defining the nature of the lesion. USG shows bulky submandibular gland with altered echotexture or diffuse non-specific enlargement of the gland [4]. Tuberculous foci in the gland appear as hypoechoic lesions. USG can also pick up enlarged multiple necrotic submandibular lymph nodes [4]. Ultrasonography is an excellent imaging modality but there are resolution limitations; therefore, computed tomography (CT) scan is often required to confirm the nature of the lesion.

CT scan typically detects lesion greater than 0.5 cm in diameter. There is no specific CT scan finding suggestive of TB. CT scan shows enlarged submandibular gland with diffuse fat stranding [8]. The lesion appears as inflammatory hypodense mass and in an acute lesion there may be associated thickening of overlying subcutaneous tissue and skin and loss of fat planes with surrounding muscles [8]. Enlarged lymph nodes appear hypodense suggestive of necrosis. In nodular type of involvement, CT scan shows homogenously enhancing gland with or without contrast enhancing round areas. CT findings suggestive of TB are multiple, round, smooth walled rim enhancing lesion with central lucency within the gland with parenchyma showing enhancement and filling defect [13, 14]. It is extremely difficult to differentiate mycobacterial inflammatory lesions of submandibular gland from neoplastic masses by CT alone. Magnetic resonance imaging (MRI) is an expensive study used mainly for assessment of the ductal system of the salivary glands by MR sialogram [14].

Role of Fine Needle Aspiration Cytology (FNAC)

This is the study of choice for diagnosing submandibular gland TB. It is cheap, non-invasive and safest method. Kim et al. reported that the diagnostic accuracy is 33.3% [15]. Iseri et al. concluded that the sensitivity of FNAC is 81–100% and specificity is 94–100% in salivary gland lesions [16]. Virmani et al. reported that the sensitivity of

FNAC in detecting TB of salivary glands is 71.4% and USG can increase the yield of aspirate [4].

Role of Acid-Fast Bacilli (AFB) Staining, Culture and Polymerase Chain Reaction (PCR)

The saliva, aspirate and tissue can be used for AFB staining, culture and PCR assay. The sensitivity of AFB staining and culture is 28.6%; low for diagnosis of EPTB [4]. Combining FNAC and culture increase the diagnostic yield to 85.7% [4]. The sensitivity and specificity can reach to 90% if FNAC is combined with PCR [8, 10, 17]. The advantages of PCR assay are its ability to produce rapid results and it is easy to perform as compared to staining and culture. The drawbacks of PCR assay are its false positivity, high cost, low availability and inability to differentiate live and dead organisms [15, 18, 19].

Role of Incisional/Excisional Biopsy

Incisional biopsy is contraindicated as it can lead to chronic fistula formation [8]. Excisional biopsy is indicated when the level of suspicion is high because of clinical presentation, epidemiological features, and imaging studies; and repeat FNAC and other non-invasive methods fail to diagnose TB [12, 20].

Differential Diagnosis

Tuberculous lesions of submandibular gland are most commonly mistaken for benign non-granulomatous masses and malignant masses of submandibular gland. Granulomatous lesions such as cat scratch disease, sarcoidosis, actinomycosis, scleroma and amyloidosis also form important differential diagnosis.

The details of all the published cases and case series are given in Table 2 and the conclusion of three case series is given in Table 3.

Management

There are no specific guidelines for management of submandibular gland TB because of the rarity of disease. Once a correct diagnosis has been made, it is curable with standard short-course antituberculous treatment (ATT) [4, 6, 8]. Therefore, every effort should be made to diagnose this medically curable disease without surgical intervention. Treatment regimen consists of combination of four drugs- isoniazid (5 mg/kg BW/day), rifampicin (10 mg/kg BW/day), pyrazinamide (30 mg/kg BW/day), ethambutol (20 mg/kg Bw/day) for 2–4 months, subsequently isoniazid and rifampicin for 6–12 months [6, 19]. Isolated EPTB is associated with lower bacillary burden than pulmonary disease. Therefore, isolated EPTB such as submandibular gland tuberculosis needs be treated with standard short-course regimens that are effective for pulmonary disease [6, 7, 8, 20]. However, disseminated disease with tuberculous submandibular gland involvement needs to be treated with 12 months antituberculous chemotherapy [6, 7, 8, 19, 20]. During each follow up visit, detailed history focusing on improvement in symptoms and clinical signs is important. USG is the study of choice for follow up, in guiding the duration of ATT, and also in guiding about the need of any form of surgical intervention during medical therapy.

Indications of Surgical Intervention

1. Tuberculous abscess- USG-guided aspiration is preferred modality of management.
2. Excisional biopsy if diagnosis cannot be made on non-invasive methods.
3. Non-responsive disease or failed medical therapy.
4. Enucleation for residual enlargement of the gland for cosmetic reason.
5. Tuberculous lesion associated with calculi in Wharton's duct.

Conclusion and Recommendations

TB of major salivary glands is rare a rare form of EPTB. TB of parotid gland is more common than submandibular gland. Primary and isolated TB of submandibular gland is extremely rare. Secondary involvement of submandibular gland from an adjacent tuberculous focus is more common; though in majority of cases it is difficult to document the specific source of focus. The authors recommend:

1. Pre-operative diagnosis of submandibular gland TB is difficult. Consider the possibility of TB in a relatively young patient with a painless mass lesion in the submandibular gland of long duration, patient who comes from areas with high incidence of active TB, active or past history of pulmonary TB, history of TB contact, patients with congenital or acquired immune deficiency.
2. Laboratory tests such as raised ESR, positive Montoux test may be a pointer towards diagnosis. PCR assay is helpful in diagnosis. Imaging studies show a mass lesion in the submandibular region with or

Table 2 Details of previously reported cases

Author (year) (reference)	No. of cases	Clinical presentation	Age /sex	Past history of TB/TB contact	Associated comorbidity	HIV status	Imaging study	Culture/ PCR assay/ FNAC/ incisional biopsy / Excisional biopsy
Kumar et al. (1990) [1]	1	–	–	–	–	–	–	–
Tsutomu et al. (1999) [19]	1	Painful swelling, abscess	45/F	No	No	–	CXR-N, CECT-suspicion of malignancy	Excisional biopsy positive
Kim et al. (2005) [15]	3	–	–	No	No	Negative	CXR-N	FNAC positive in 1, PCR in 1, Excision in 1
Moure et al. (2006) [17]	1	–	–	No	No	Negative	CXR-N	Excisional biopsy
Bottini et al. (2007) [7]	1	Painless swelling	15/M	No	No	Negative	CXR-N	Excisional biopsy positive
Tauro et al. (2011) [8]	2	Case 1: painful swelling-1 month	Case 1: 45/M	No	No	Negative	CXR-N, CECT-inflammatory hypodense mass	FNAC-negative, Incisional Bx-positive
		Case 2: painful swelling- 2 months	Case 2: 25/M	No	No	Negative	CXR-N	FNAC-positive, PCR- positive
Dadwal (2011) [19]	1	Gradually increasing painless swelling-1 year	35/F	No	No	Negative	CXR- N	FNAC- positive, PCR assay positive, culture- negative
Kasim et al. (2015) [10]	1	Gradually increasing swelling, occasional pain, low grade fever-1 month duration	36/M	No	No	Negative	CXR- N, CECT-4 cm swelling, inhomogenous suggestive of tumor	Saliva culture positive for TB, FNAC negative, PCR not done, excision of gland-HPE positive for TB
Virmani et al. (2019) [4]	4	Painful swelling in 2 cases, painless swelling in 2 cases-2 months	–	No	No	Negative	USG showed bulky submandibular gland with altered echotexture	Culture positive in one case, FNAC positive in three cases, excisional biopsy positive in one case

– not available; *Tb* tuberculosis; *CECT* contrast enhanced computed tomography; *CXR* chest X-ray; *FNAC* fine needle aspiration cytology; *PCR* polymerase chain reaction; *HIV* human immunodeficiency virus

Table 3 Conclusion of various case series

Author (year) (reference)	Number of cases	Conclusion
Kim et al. (2005) [15]	3	Tuberculosis of the salivary gland is mostly a medically curable disease entity but early diagnosis is very important to ensure complete remission. In cases with high index of suspicion, polymerase chain reaction should always be considered before surgical intervention
Tauro et al. (2011) [8]	2	Polymerase chain reaction is a reliable diagnostic tool, and if available, it should be performed before surgical intervention to enable differential diagnosis of a salivary gland tumor
Virmani et al. (2019) (4)	4	Primary tubercular sialadenitis is a rare entity with a myriad of clinical presentation. A index of suspicion, early diagnosis, and timely institution of antituberculosis treatment is essential for estabilishing a cure

without associated necrotic lymph nodes. FNAC is diagnostic. Proceed with FNAC combined with culture and PCR assay to increase the diagnostic yield in suspected cases.

3. Incisional biopsy should not be done. Try and make all efforts to diagnose it without major surgical intervention as this pathology responds well to ATT. To achieve a definite diagnosis without surgical intervention, symptoms, clinical signs and epidemiological features should be correlated with laboratory and imaging study findings.
4. Surgical intervention is indicated for non-responsive disease and complications.

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