Lingual tuberculosis: a rare disease in Western countries

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SUMMARY

Here we report on two consecutive cases of tuberculosis in immunocompetent HIV-negative patients with lingual lesions. In both patients diagnosis was delayed. Disease progressed involving the lungs, lymph nodes and also the brain. Both patients are disease-free at 30 and 22 month follow-up respectively. Isolated *Mycobacterium tuberculosis* from these patients was multi-susceptible. Tuberculosis lesions of the oral cavity and brain are infrequently diagnosed in immunocompetent subjects from Western countries. Clinicians must take into greater consideration tuberculosis as a possible diagnosis when diagnosing chronic and/or recurrent lingual lesions even in the absence of pulmonary lesions.

KEY WORDS: Tongue tuberculosis, Tongue ulceration, Brain tuberculomas, Brain mass lesions, Anti-tuberculosis therapy, Immunocompetent patients

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INTRODUCTION

Lingual tuberculosis (TB) is rare and accounts for 0.5-3% of all cases of extrapulmonary TB. It is more frequently diagnosed in immunocompromised patients, males and smokers. It is commonly secondary to contact with infected respiratory secretions or hematogenous dissemination of *Mycobacterium tuberculosis* (Kakisi *et al.*, 2010; Gupta *et al.,* 2011; Mignogna *et al.,* 2000; Gharebaghi *et al.,* 2011). Rarely is it due to direct inoculation. Primary oral tuberculosis is more common in younger patients (Kakisi *et al.,* 2010; Kumar S *et al.,* 2010; Sharma *et al.*, 2008). TB lesions of the oral cavity are infrequent in Western countries (Kakisi *et al.,* 2010; Gupta *et al.,* 2011; Mignogna *et al.,* 2000; Gharebaghi *et al.*, 2011). Diagnosis requires searching for *M.tuberculosis* in lingual biopsy or searching for other sites of tuberculosis (Kakisi *et al.*, 2010; Sharma *et al.*, 2008; Mignogna *et al.,* 2000; Gharebaghi *et al.,* 2011).

This paper reports on two consecutive cases of lingual tuberculosis progressing to disseminated disease involving the lungs, lymph nodes and the brain.

CASE REPORT 1

A 57-year-old immunocompetent male smoker from Moldova who had been living in Italy for the last six years underwent a biopsy for an ulcer in the left posterior part of his tongue in February 2005. The patient did not report a history of tuberculosis. Histopathology disclosed necrosis and chronic granulomatous reaction with giant cells. Healing was obtained after a two week course of moxifloxacin. Over the following months, the patient relapsed twice: both episodes

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were cured with moxifloxacin. Two years later (Figure 1), in October 2007, at the fourth relapse, fever, night sweating and a weight loss of 13 kilos were reported while moxifloxacin was ineffective. Computed tomography (CT) disclosed a solid mass with necrosis and liquefaction extending to the left amygdalo-glosso sulcus, the tonsillar loggia, the floor of the mouth, sublingual lymph nodes and the digastric muscle. Furthermore, irregular left lingual borders were present. Chest radiograph depicted bilateral reticulo-nodular infiltrates. A second lingual biopsy confirmed the results of the first, plus the presence of acid fast bacilli (AFB). AFB were also detected in the bronchial alveolar lavage fluid, while molecular amplification test was positive for *M. tuberculosis* complex (Mazzarelli *et al.,* 2003). Multi-susceptible *M. tuberculosis*, including moxifloxacin, was grown from respiratory and urine specimens. Isoniazid, pyrazinamide, ethambutol and rifampin were prescribed and continued for the first 4 months, followed by isoniazid and rifampin for the remaining 10 months of therapy. HIV-1 and HIV-2 antibodies were negative. Tuberculosis skin test was 12 mm and gamma interferon assay (IGRA) was positive. After two weeks of treatment, pain, fever and sweating subsided, the ulcer was reduced and the patient gained 4 kilos. Thus, the patient was discharged. Three weeks later, the patient was readmitted complaining of headache, psychomotor agitation, altered visual acuity and dysarthria without fever. On examination, the ulcer had healed and the patient had regained another 8 kilos. He was alert, oriented, did not have meningeal signs but, dysarthria, lateral deviation of the lingual and imbalance were present. Brain CT showed multifocal mass lesions in the cortical subcortical cerebral hemispheres, cerebellum and pons. These lesions were hypointense on T1 weighted magnetic resonance imaging (MRI) and hyperintense on fluid-attenuated inversion recovery (FLAIR) and T2 MRI, showing ring enhancement and perifocal edema. Cerebralspinal fluid was normal and Zhiel-Neelsen, molecular amplification test and culture for *M. tuberculosis* were all negative. Chest radiograph showed reduced micronodular infiltrates. The patient refused a brain biopsy. The neurological manifestations were interpreted as being due to a paradoxical worsening of pre-existing silent brain tuberculomas during effective TB treatment (Semlali *et al.,* 2008; Teoh *et al.,* 1987; 2005; Rock *et al.,* 2008). Prednisone 50 mg/die and mannitol infusion were started (Teoh *et al.*, 1987; Ripamonti *et al.*, Rock *et al.,* 2008). Within one week, the clinical condition improved

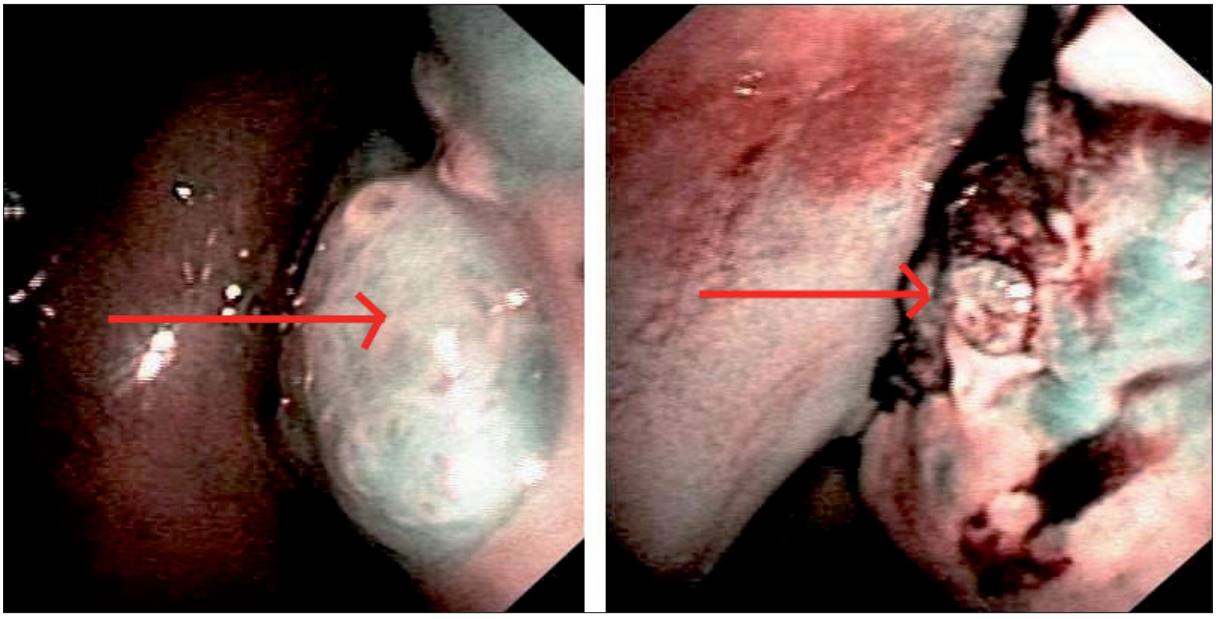

FIGURE 1 - *Case report 1: Bronchoscopy showing multi lobulate, high vascularized lesion in the posterior lateral left side of the tongue (arrows).*

and a second MRI, performed thirteen days later, showed a significant reduction in lesion size and edema. Prednisone was tapered and continued for a total of 2 months along with anti-TB therapy. Anti-TB treatment was stopped after 14 months when a further chest CT and brain MRI resulted normal and the tongue was clinically free of lesions. At 30 month follow-up the patient remains disease free.

CASE REPORT 2

A 55-year-old immunocompetent Italian male non-smoker for the last 25 years, having dry cough over the last two months underwent tongue biopsy at the base on the right side in September 2008 for a papillomatous asymptomatic lesion. The patient reported no history of tuberculosis. Tongue biopsy revealed granulomatous reaction, giant cells without necrosis and no tumor cells. Neck CT disclosed two right cervical large lymph node masses having necrosis and a hypertrophic lymphatic ring. Chest radiograph was negative. During hospital stay the patient was treated with piperacillin 2 g IM twice a day and the same therapy was prescribed for another week. Two months later, cough and cervical lymph node enlargement persisted plus fever. A second chest radiograph was performed and showed a left apical infiltrate without cavity. At this point, levofloxacin 500 mg daily was administered. A bronchial alveolar lavage fluid and a lymph node biopsy showed AFB. The molecular amplification test for *M. tuberculosis* complex was positive in both samples. HIV-1 and HIV-2 antibodies were negative. Tuberculosis skin test was not reported while IGRA was positive. Isoniazid, rifampin, ethambutol, pyrazinamide were started on November 26, 2008 and continued for 4 months, followed by isoniazid, rifampin and pyrazinamide over the next 2 months and isoniazid and rifampin for the remaining 6 months. In conclusion, anti-Tb therapy was administered for a total of 12 months. Fever and cough subsided, Zhiel Neelsen and sputum cul-

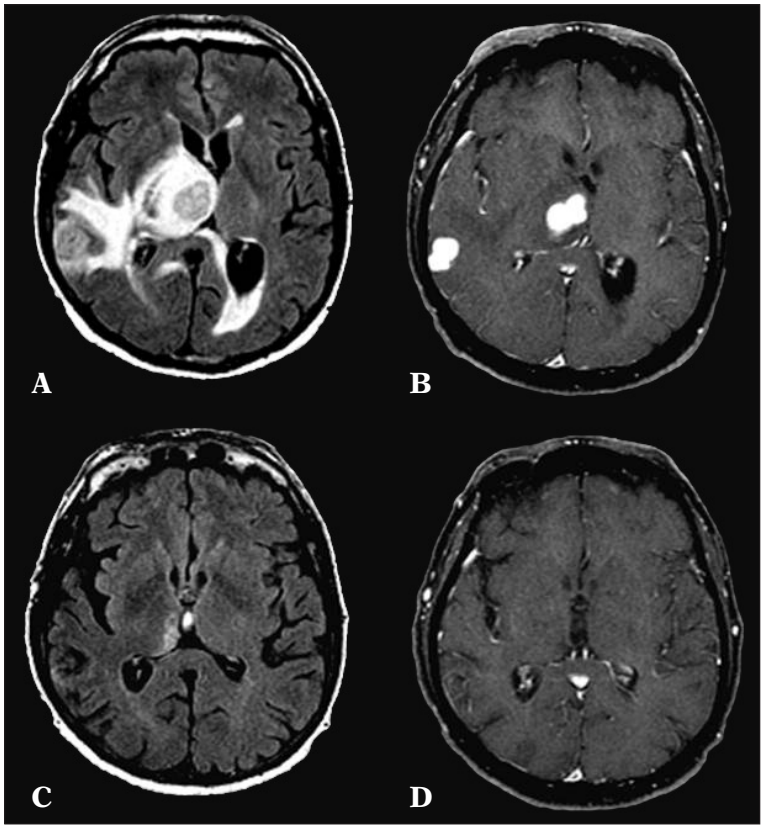

FIGURE 2 - *Case report 2: (A) fluid-attenuated inversion recovery (FLAIR) MRI image showing hyperintense non caseous nodules with surrounding edema in the right temporal lobe and thalamus, (B) homogeneous contrast enhancement on T1 MRI. MRI images three months later with anti-TB treatment without corticosteroids: (C) minimal edema, (D) absence of contrast enhancement.*

ture became negative after 3 weeks of anti-TB therapy, cervical lymph nodes decreased in size and laboratory results (erythrocyte sedimentation rate, α2-globulin, C-reactive protein) improved. In the absence of neurological symptoms, in view of the clinical course of case 1, a brain MRI was performed (January 2009) showing numerous enhanced mass effect nodules. The largest nodules had central necrosis and were located in the right thalamus and had marginal mesencephalic involvement. Other lesions were present in both the temporal and occipital right lobes, the frontal lobes, right cerebellum and the bulb (Figure 2A and 2B). An MRI, three months later, showed almost complete disappearance of the lesions and edema (Figure 2C and 2D). At 22 month follow-up the patient was clinically, microbiologically and radiologically free of disease.

DISCUSSION

Initial clinical observation of lingual lesions and cervical lymphadenopathy in middle-aged patients suggested cancer. Lingual lesions can also be caused by several other diseases including TB (Gharebaghi *et al.,* 2011). Worldwide lingual TB is rare and when occurring, the dorsal surface is more commonly involved (Kumar *et al.,* 2010). Oral, including lingual TB, is more commonly secondary to contact with infected respiratory secretions or hematogenous dissemination. Very rarely is it due to direct inoculation of *M. tuberculosis* and this pathogenesis is more frequent in children and adolescents. Lingual ulcerations are the most frequent presentation but oral TB may involve other parts of the oral cavity and have diverse manifestations (Kakisi *et al.*, 2010). Lingual lesions, like other oral cavity TB lesions, have non-specific symptoms or can even be asymptomatic so that the diagnosis of lingual TB may be overlooked (Kumar *et al.,* 2010, Kakisi *et al.,* 2010, Mignogna *et al.*, 1999). In both of our cases diagnosis was delayed and successfully made only after AFB were seen in the bronchial alveolar fluid of Case 1 and the bronchial alveolar fluid plus lymph node tissue in Case 2. At diagnosis, both patients had already developed a disseminated TB and intracranial seeding of *M. tuberculosis* leading to brain tuberculomas.

Brain mass lesions due to *M. tuberculosis* are also rare in countries with low TB endemicity (Ripamonti *et al.,* 2004; Nicolls *et al.,* 2005; Rock *et al.,* 2008). Most cases have been reported in non-Caucasians, immunocompromised patients, children or persons with miliary or meningitis TB and can manifest while the patient is being treated for tuberculosis (Teoh *et al.,* 1987; Ripamonti *et al.*, 2004; Nicolls *et al.,* 2005; Rock *et al.,* 2008; Garg *et al.,* 2010). The diagnosis and management of these tubercular manifestations are also problematic (Teoh *et al.,* 1987; Ripamonti *et al.,* 2004; Nicolls *et al.,* 2005; Rock *et al.,* 2008). In Case 1, neurological clinical signs developed 36 days after successful anti-TB treatment. Literature has reported extensively on this paradox (Teoh *et al.,* 1987). This expansion of cerebral tuberculomas has been reported to occur most frequently in non-Caucasian patients and on average two months after the start of anti-TB treatment (Teoh *et al.,* 1987). After drug resistance or poor compliance with treatment have been excluded, it has been hypothesized that small intracranial tuberculomas, non-visible with radiology studies, can be present at the onset and enlarge when the patient is being treated (Teoh *et al.,* 1987). The most commonly accepted explanation for this phenomenon is that there is an inflammatory response caused by the killing of *M. tuberculosis* with anti-tuberculosis drugs causing release of tuberculoproteins (Teoh *et al.,* 1987). Moreover, it is plausible that a reinvigorated immune system, due to effective anti-TB treatment, contributes to this phenomenon, as seen in immune restoration of HIV patients with active antiretroviral therapy (French *et al.,* 2000). Corticosteroids or surgical decompression have been indicated to control this reaction (Teoh *et al.*, 1987; Ripamonti *et al.,* 2004; Nicolls *et al.,* 2005; Rock *et al.,* 2008; Garg *et al.,* 2010).

Case 2 was an Italian male non-smoker with no apparent risk factors for and no reported history of TB. As in Case 1, this patient also manifested lingual TB followed by lymph node, non miliary pulmonary TB and brain tuberculoma on MRI at the 42nd day of anti-tuberculosis treatment. As there were no neurological clinical symptoms, steroids were not added (Nicollos *et al.,* 2005).

The choice of an anti-tuberculosis drug treatment depends on the susceptibility of *M. tuberculosis* and its possible side-effects. *M. tuberculosis* isolated from these two cases was multi-

susceptible therefore first-line anti-tubercular therapy was administered and there were no side-effects. Regarding duration of treatment in patients with extrapulmonary TB involving the oral cavity, the mean time from available reports ranged from 6 to 15 months (Kakisi *et al.,* 2010). Likewise, there are no clear guidelines on the recommended time also for CNS TB involvement (Ripamonti *et al.,* 2004).
Despite the delayed diagnosis both patients are disease free at 30 and 22 month follow-up respectively.

CONCLUSIONS

Worldwide, lingual tuberculosis is rare. Clinicians must take tuberculosis into greater consideration as a possible diagnosis when diagnosing chronic and/or recurrent lingual lesions even in the absence of pulmonary TB.

REFERENCES

French M.A., Lenzo N., John M., Mallal S.A., Mckinnon E.J., James I.R., et al. (2000). Immune restoration disease after the treatment of immunodeficiency HIV-infected patients with highly active antiretroviral therapy. *HIV Med.* **1**, 107-115.

Garg R.K., Sharma R., Kar A.M., Kushwaha R.A.S., Singh M.K., Shukla R., et al. (2010). Neurologic complications of miliary tuberculosis. *Clin. Neurol. Neuros.* **112**, 188-192.

Gharebaghi N, Monsouri SA, Darazam IA, Mansouri D, Sajadi MM, Mansouri N. (2011). A 40-year old man with tongue lesions. *Clin. Infect. Dis.* **52**, 1276-1277.

Gupta S., Vineeth N.S. (2011). Oro-lingual tuberculosis: a forgotten entity. Report of a case and review of literature. *J. Int. Oral Health.* **3**, 31-35.

Kakisi O.K., Kechagia A.S., Kakisis I.K., Rafailidis P.I., Falagas M.E. (2010). Tuberculosis of the oral cavity: a systematic review. *Eur. J. Oral. Sci.* **118**, 103-109.

Kumar S., Sen R., Rawal A., Dahiya R.S., Dalal N., Kaushik S. (2010). Primary lingual tuberculosis in immunocompetent patient: a case report. *Head Neck. Pathol.* **4**, 178-180.

Mazzarelli G., Rindi L., Piccoli P., Scarparo C., Garzelli C., Tortoli E. (2003). Evaluation of the BDProbeTec ET system for direct detection of *Mycobacterium tuberculosis* in pulmonary and extrapulmonary samples: a multicenter study. *J. Clin. Microbiol.* **41**, 1779-1782.

Mignogna M.D., Munzio L.L.O., Favia G., Ruoppo E., Sammartino G., Zarrelli C., et al. (2000). Oral tuberculosis: a clinical evaluation of 42 cases. *Oral Dis.* **6**, 25-30.

Nicolls D.J., King M., Holland D., Bata J., Del Rio C. (2005). Intracranial tuberculomas developing while on therapy for pulmonary tuberculosis. *The Lancet Infect. Dis.* **5**, 795-801.

Ripamonti D., Barbò R., Rizzi M., Finazzi M.G., Ravasio L., Bonaldi G., et al. (2004). New times for an old disease: intracranial mass lesions caused by *Mycobacterium tuberculosis* in 5 HIV-negative African immigrants. *Clin. Infect. Dis*. **39**, e35-45.

Rock R.B., Olin M., Baker C., Molitorr W., Peterson P.K. (2008). Central nervous system tuberculosis and clinical aspects. *Clin. Microbiol. Rev.* **21**, 243-261.

Semlali S., El Kharras A., Mahi A., Hsaini Y., Benameur M., Aziz N., et al. (2008). Les aspects en imagerie de la tuberculose du système nerveux central. *J. Radiol*. **89**, 209-220.

Sharma A.B., Laishram D.K., Sarma B. (2008). Primary tuberculosis of tongue. Indian. *J. Pathol. Microbiol*. **5**, 65-66.

Teoh R., Humphries M.J., O'Mahony G. (1987). Symptomatic intracranial tuberculoma developing during treatment of tuberculosis: a report of 10 patients and review of the literature. *Quart. J. Med.* **241**, 449-460.