Case Report

Primary oral tuberculosis following dental extraction in a patient undergoing hemodialysis: A case report

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Primary oral tuberculosis after dental extraction is almost non-existent, and there is very little data on its clinical, pathological and radiological features. A 34 year-old Turkish man in good condition was treated with known chronic renal failure due to hypertension and who had been undergoing maintenance hemodialysis, 3 times a week for 3 months. He presented with swelling of the submental region following two teeth extractions diagnosed as teeth abscesses. Following the biopsies from the lesions, the histopathological findings, an analysis of the positive culture, demonstrated mycobacterial cord factor and polymerase chain reaction response to the Mycobacterium confirmed primary oral tuberculosis after dental extraction. The patient had no evidence of tuberculosis anywhere else in his body. Medical and periodontal treatment were curative. This case highlights the importance of considering tuberculosis because of (1) the rarity of primary oral tuberculosis after dental extraction, (2), the presence of the Mycobacterium cord factor is considered as a virulence factor in the Mycobacterium tuberculosis, (3) the patient’s being young and in good condition displayed a favourable response to anti-tubercular and periodontal treatment.

Key words: Primary, oral tuberculosis, dental extraction.

INTRODUCTION

Tuberculosis (TBC) is still one of the most life-threatening infectious diseases, resulting in high mortality in adults (World Health Organization, 2008). Patients receiving chronic hemodialysis are more susceptible to tuberculosis (TBC) and other infections than the general population. This is attributed to impaired cellular immunity and other immunologic abnormalities associated with chronic renal failure (CRF) (Cengiz et al., 1988). The diagnosis of the TBC may be complicated in patients, with CRF because they often have a typical clinical presentation of TBC, a negative tuberculin skin test, nonspecific symptoms that may be attributable to CRF, and a higher occurrence of extrapulmonary TBC compared with other patient populations (Cengiz, 1996; Cengiz and Şeker, 2006). Reports from Turkey and Saudi Arabia report incidence of 23.6% and 28% of TBC in hemodialysis patients in areas with an overall prevalence of 1% (Cengiz, 1996; Mitwalli, 1991). Also, it is evident that patient with CRF will comprise an increasing proportion of the dental patient population in the future (Craig, 2008).

Oral TBC has been considered to account for 0.1 to 5% of all TBC infections, based on reviews published before 1950. Nowadays, oral manifestations of TBC are reappearing alongside with many forgotten extrapulmonary infections as a consequence of the outbreak and emergence of drug-resistant TBC and of the emergence of acquired immuno-deficiency syndrome (AIDS), where oral TBC is found to account for up to 1.33% of human immunodeficiency virus (HIV) associated opportunistic infections, based on a cohort of 1,345 patients (Miziara, 2005). Unfortunately, the magnitude of this phenomenon in immunosufficient hosts and the patients with CRF on dialysis have not been studied in detail. It is true that the
dental identification of Mycobacterium tuberculosis has the potential to serve as an important aid in the first line of control for this dangerous, and often fatal disease. Its scarcity and frequent change of being overlooked during routine intraoral examination make it worthy of documentation. Nevertheless, TBC lesions of the oral cavity are rare and there can be a diagnostic challenge, particularly in young immunocompetent patients. In rare cases TBC spreads from the pulmonary system to the oral cavity, in extremely rare cases it is confined solely to the oral cavity (Mignogna et al., 2000; Ebenezer et al., 2006; Rivera et al., 2003; Ito et al., 2005). A review of literature revealed only two cases of primary oral TBC after dental extraction (Selimoğlu et al., 1995; LoBello et al., 1984).

The presumptive identification of M. tuberculosis using the macroscopic evaluation of colonies combined with cord, a virulence factor detection under microscopy is a simple, rapid and inexpensive test. The aggregation of mycobacterial cells in a definite order, forming microscopic structure that resemble cords, is known as cord formation, or cording, and is considered a virulence factor in the M. tuberculosis complex and the species Mycobacterium marinum. M. tuberculosis microscopic cords were first observed by Robert (1882), but knowledge of their significance increased according to the studies of Middlebrook et al. (1947). These authors compared the virulent H37Rv and avirulent H37Ra M. tuberculosis strains and found that the formation of cords took place only in the virulent strain, whereas cells from the avirulent H37Ra strain were not oriented and merely formed irregular clumps. In 1953, block isolated a toxic glycolipid from M. tuberculosis and related it to the virulence of the tubercule bacillus and the cording. Microscopic cords today are considered to be related to virulence.

The purpose of this article is to emphasize the importance of early diagnosis of primary oral TBC after dental extraction of the patient with CRF undergoing hemodialysis, which may be misdiagnosed when oral lesions are not associated with any apparent systemic infection.

To the best of our knowledge, this is the first case report that documented well the primary oral TBC after dental extraction in the patient with CRF undergoing hemodialysis.

CASE REPORT

A 34 year old Turkish male patient admitted in the hospital with gradually increasing swelling of the right jaw and fever.

The patient complaining of pain in the oral cavity especially, on the right side of the mandibula, buccal mucosa, had difficulty in chewing and swallowing solid food. He had intermittent fever and gradually increasing swelling which started to develop over a month. He had difficulty in eating and complained of some teeth mobility, and gum bleeding. He had no previous history of a serious illness, chronic cough with expectoration or other chest symptoms and weight loss. His appetite was normal. A dental extraction a month earlier was noted. He claimed that his teeth ached a lot and 2 teeth were extracted by a dentist after being diagnosed as teeth abscesses.

In his past medical history, he explained that his gums started bleeding at very early age. At the age of 22, he had been diagnosed with chronic periodontitis. Nonetheless, he had neither seen any dentist for this problem nor performed any personal oral hygiene. The patient presented hypertension for approximately 12 years. Also his father, two brothers and one sister were hypertensive. The patient had chronic renal failure due to hypertension and was on maintenance hemodialysis, 3 times a week for 3 months. He did not have any systemic complaints and medications, except antihypertensive drugs and he had no history of any allergy, in that he was a nonsmoker. The patient was a primary school graduate and a workman in the municipality. All the family are farmer who lived together in a rustic area. Their sociocultural and socioeconomic conditions were poor.

Because an infection was suspected, he had been treated with amoxicillin for a week in a private practice, without success.

A physical examination revealed that the patient was in good condition and febrile (38°C). Extraorally, a firm tender swelling of the right side of the mandible extending from the body to the angle was observed (Figure 1). The right submandibular lymphnodes which had not enlarged before, became mobile and nonfender to palpation. Intraoral examination revealed a generalized chronic periodontitis with bleeding on probing and decays. His oral hygiene was graded as poor with generalized mobility of all the teeth and moderate depostits of stains were present throughout the dentition. Almost all of his teeth had some degree of attrition and some of his teeth were clinically missing. Oral examination showed that the lower right first molar and the upper right second molar were extracted. Mean remaining teeth pocket depth was probed 4.2±0.7 mm (pocket depth was probed up to 5 mm). There were small fissures, swelling and a few nodules less than 0.5 cm in diameter on the right buccal mucosa. The ulcer was bordered by well defined margins around which there were several nodular swellings. On palpation, the ulcer was tender with indurated margins. The culture from the fissures, purulent exudate and ulcer were negative. Necrotic tissue and predomination of polymorphonuclear cells were present throughout the ulcer. The buccal mucosa was reddened and edematous. The marginal gingiva was thickened. There was a wide undermining along the palatal gingiva.

Intraoral examination revealed a generalized chronic periodontitis with bleeding on probing and decays. His oral hygiene was graded as poor with generalized mobility of all the teeth and moderate deposits of stains were present throughout the dentition. Almost all of his teeth had some degree of attrition and some of his teeth were clinically missing. Oral examination showed that the lower right first molar and the upper right second molar were extracted. Mean remaining teeth pocket depth was probed 4.2±0.7 mm (pocket depth was probed up to 5 mm). There were small fissures, swelling and a few nodules less than 0.5 cm in diameter on the gingiva. Purulent exudate in the affected area was present. Also, there were buccal folds towards the extracted teeth. Soft tissue examination revealed a single discrete ulcer less than 0.5 cm in diameter on the right buccal mucosa. The ulcer was bordered by well defined margins around which there were several nodular swellings. On palpation, the ulcer was tender with indurated margins. The culture from the fissures, purulent exudate and ulcer were negative. Necrotic tissue and predomination of polymorphonuclear cells were present throughout the ulcer. The buccal mucosa was reddened and edematous. The marginal gingiva was thickened. There was a wide undermining along the palatal gingiva.
leucocytes were detected in smear tests taken by sterile paper pad from pockets and extraction sockets. Enlargement of the of the regional lymphnodes and soft tissue mass were seen and swelling on the right side of his submandibular region gradually increased and did not respond to conservative and antibiotic therapy.

Some laboratory findings at admission were following: Hb 11.4 g/dl, white blood cell (WBC) count 12.400/ mm³, blood urea nitrogen (BUN) 38.6, serum creatinine 5.7 mg/dl, erythrocyte sedimentation rate (ESR) 104 mm/h, high sensitive C-reactive protein (CRP) concentration was elevated at 8.2 mg/dl (normal range< 1.0). Serum Ig A, Ig G, Ig M, C₃, C₄ and lipid levels were within the normal limits. Also, routine biochemical tests including total proteins and albumin levels in urine analysis were within normal limits. After the initial clinical evaluation, it is thought that one of the diseases, namely dentoalveolar abscess, tuberculosis, viral or fungal infection could cause the patient’s illness. Routine laboratory investigations were grossly unmarkable with only the ESR and hs CRP being remarkably high. Further investigations were carried out, including sputum examination, echocardiography, abdominal ultrasonography, abdominal tomography, peripheral blood smear, chest screening, enzyme-linked immunosorbent assay for HIV 1 and 2, and purified protein derivative (PPD) skin test, direct smear and culture in the oral cavity for bacteria, virus and fungus were all negative. Because chest screening and PPD tests were negative, all the cultures from blood, urine, various places in the oral cavity were taken several times for bacteria, virus and fungus and they were all negative as well. The patient was treated with empirical regimen of intravenous cefotaxime, a third generation cephalosporin for 6 days before coming to the hospital. Ten days after treatment he felt worse, with intermittent spiking fever (38.5°C). So, cefotaxime was changed to intravenous imipenem plus vancomycine for one week without success. Then further investigations were carried out as follows: a panoramic radiography of his mandibule showed a normal bony configuration. There were no destructive changes in the bone (Figure 2). Chest reontgenography revealed no findings suggestive of TBC or any other infection (Figure 3). Whole body bone scan and SPELT/CT of the head were performed 3 h after injection of 740 mega becquerel (MBq) Tc-99m methylene diphosphate (Tc-99m MDP). No pathological finding was detected except for a focal accumulation of radiopharmaceutical in the right part of the mandibula and maxilla that might be due to infection and/or tooth extraction. Except an increased osteoblastic activity was found during bone scan (Figure 4). Computed tomography (CT) of the mandibula; axial contrast enhanced CT scan showed a 3 cm diameter mass next to the right submandibular gland with central hypodensity and peripheral enhancement suggesting a suppurative lymphnode. It was noted that there was a thickening of the skin and an increase in heterogenous density in subcutaneous fat tissue adjacent to the lesion. There are also smaller sized lymphnodes medial to the lesion (Figure 5). Magnetic resonance (MR) of the mandibula; axial T2 weighted MR image showed a solid lesion (arrow) hyperintense relative to adjacent fat tissue located anterior to the right submandibular gland and minimal fluid intensity around it (Figure 6). Needle aspiration from
Figure 3. Chest radiograph without abnormal findings.

Figure 4. Planar and SPECT/CT images of the head show focal increased osteoblastic activity in the mandible (arrow) and maxilla (arrowhead).
the mass was performed and cytology showed that necrotic material and inflammation. Also, cultures were negative for bacteria, fungus and viruses.

Finally, an incisional biopsy of the mass and needle biopsies were carried out. Incisional biopsy from the mass was performed on the 21st day of the patient’s hospitalization. Surgical curative materials were examined from extraction sockets, granulation tissues and a small nodule close to the extracted sockets, fissures close to extracted teeth, and pocket depths. Histopathological examination revealed a chronic granulomatous lesion consisting of multiple granulomas, epithelioid histiocytes, histiocytic giant cells and caseification necrosis, highly suggestive of TBC (Figures 7a and 7b). The special stain, Ziehl-Nelson staining and conventional tissue culture in Lowenstein-Jensen media were positive. Moreover, in order to confirm the histopathological presumptive diagnosis and to identify the different species of M. tuberculosis, polymerase chain reaction (PCR) DNA analysis was conducted, allowing us to reach the final diagnosis. Interestingly, tuberculous cord phenomenon known as viruland strains and bacilli were seen (Figures 8a and 8b).

Following the definite diagnosis of TBC, the pulmonary system was investigated extensively. All pulmonary function tests, culture and smear from the sputum, high resolution computed tomography (HRCT), repeated chest radiography and a routine medical consultation were requested. All of which turned out to have negative results for the other mycobacterial foci except for in the oral cavity. Further investigation of the patient’s family history revealed negative results for TBC as well.

Afterwards the patient received comprehensive periodontal therapy, which included careful oral hygiene instructions, curettage combined with non-surgical therapy. The patient was then referred to the chest department where he began a combination of 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) administered daily for, the first 3 months, followed by additional 9 months with 2 drugs (isoniazid and rifampicin). The total duration of therapy is still a matter of debate. Recovery took two years during which the mass had disappeared, ESR and hs-CRP were within the normal limits. The patient was registered for renal transplantation. No recurrence of the lesion occurred during 2 year follow-up.

**DISCUSSION**

Oral manifestations of TBC are uncommon, observed only in 0.05 to 5% of patients with TBC (Mignogna et al., 2000). Primary involvement of the oral cavity is exceedingly rare; therefore, it has been described only in case reports. To the best of our knowledge, this is the first case report that documented well the primary oral TBC after dental extraction in the patient which CRF undergoing hemodialysis.

The mechanism of primary inoculation into the oral mucosa is not clearly understood. The intact mucous membrane presents a natural resistance to the direct penetration by bacilli. This resistance has been attributed to the cleansing action of saliva; the presence of salivary enzymes, tissue antibodies, or oral saprophytes; and the
Figure 7. Histopathological examination revealing a chronic granulomatous lesion consisting of multiple granulomas, epitheloid histiocytes, histiocytic grain cells and caseating necrosis. (a) HEx 400, (b) HEx 200.

Figure 8. (a) PCR culture showing cord phenomenon with viruland strains and (b) cord factor and bacilli of M. tuberculosis.

thickness of the protective epithelial cavering. Any break or loss of this natural barrier, which may be a result of trauma, inflammation, tooth extraction, periodontal disease or poor oral hygiene, may lead to infection by tubercule bacilli (Hock-Liew et al., 1996; Mc Carthy et al., 1980; Dimitrakopoulos et al., 1991). Furthermore,
patients under dialysis are more susceptible to infection, because of general debilitation and depression of the immunologic response. The increased incidence of periodontitis in hemodialyzed patients is supposed to be based upon, for example, neglect of oral hygiene, increased calculus formation due to increased levels of salivary urea and other toxins. When dialyzed patients acquire acute and, subsequently, chronic gingivitis, rapidly progressing into periodontitis, their immune system is unable to fight the disease despite the treatment efforts of periodontal specialists (Craig, 2008).

In the case we presented, no evidence of lung or other systemic involvement was found, supporting the diagnosis of primary oral TBC. Furthermore, our patient had undergone two teeth extractions a month ago, after which a swelling had developed. Also, he had poor oral hygiene and the mean of his remaining teeth pocket depth had probed 4±0.7 mm (up to 5 mm). Also, at the age of 22, he had been diagnosed with periodontitis. A review of literature revealed only two cases of primary oral TBC after dental extraction (Selimoğlu et al., 1995; Lo Bello et al., 1984). The authors of these reports suggest that dental extraction, and poor oral hygiene might be the cause of the primary oral TBC. Smith et al. (1982) reported an outbreak of TBC in 15 patients following dental extraction at two community dental clinics. Out of the 15 cases, 13 had oral lesions but all of them had pulmonary TBC.

The systemic factors that favour the changes of oral infection in TBC includes lowered host resistance and increased virulence of the organisms (Nunn et al., 1994). The patients receiving chronic hemodialysis are more susceptible to TBC (Cengiz, 1996; Mitwalli, 1991). The differentiation between M. tuberculosis and nontuberculous mycobacteria is fundamental for patients co-infected with TBC and HIV. The possibility of HIV infection was ruled out, as the ELISA test for HIV 1 and 2 was negative. To that end, we detected that mycobacterial cord factor was considered a virulence factor of the PPD skin testing areas where TBC is endemic. False negative results may be strongly considered, but, direct smear and culture from oral cavity for bacteria and fungus were all negative.

For confirmation and different diagnosis, PPD reaction, biopsy for histologic examination, acid-fast stains, and culture should be obtained (Mignonga et al., 2000). Positive tuberculin skin test just indicates previous exposure to M. tuberculosis. Although presumptive diagnosis of TBC can be based on histopathological examination and identification of the bacilli in tissues using special stains and because of the relative scarcity of the bacilli within the tissue, mycobacteria can be demonstrated by means of special stains only in 27 to 60% of cases (Rivera et al., 2003). Despite the technical difficulties and lack of sensitivity that lasted 4 to 6 weeks (Mignonga et al., 2000; Rivera et al., 2003), culture of microorganisms yielded good results. Sophisticated techniques such as PCR can be used alternatively, especially when the conventional methods of diagnosis render equivocal results (Goel et al., 2001; Rivera et al., 2003).

von Arx and Husain (2001) described granulomas with sarcoid-like and numerous giant cells, some of which being the Langhans type. They raised the possibility of granulomatous infection, including TBC, or fungal infection, or a diagnosis of sarcoid. Subsequent stains for fungi (PAS and Grocott Silver) and bacteria (Gram stain) were negative. However, several acid-fast bacilli were identified with a Ziehl-Nielsen stain situated within the granulomas and considered that the infection was consistent with TBC granulomatous infections. For our case, the histopathological examination showed granulomatous inflammation containing Langhans-type giant cell and the Ziehl-Nielsen stain was positive for bacilli. In order to confirm the histopathological presumptive diagnosis and to identify the different species of M. tuberculosis, the culture was examined using the conventional and PCR-DNA methods analysis were conducted, allowing us to reach the final diagnosis. Diagnosis of the oral cavity in this case was difficult because the symptoms were nonspecific, the PPD skin test with 10 TU was negative, the patient had no evidence of TBC anywhere else in the body, so, some symptoms might be attributable to CRF. But, interestingly cord factor was positive in our patient. Conflicting results have appeared about the PPD skin test. Some authors (Andrew et al., 1980; Cengiz, 1996) claim that it is almost always negative due to suppressed cellular immunity, whilst others (Lunding et al., 1979; Hussein et al., 1990) report a positive test in 61 to 62% of their cases, respectively. However, it is difficult to estimate the value of the PPD skin testing areas where TBC is endemic. Also, PPD positive skin test indicates previous exposure to the M. tuberculosis. False negative results may be produced in immuno-compromised patients (Cengiz and Şeker, 2000). In our patient, the positive culture, PCR-DNA, histopathological tests, and mycobacterial cord factor associated with viruland strains of M. tuberculosis showed that the pathogen M. tuberculosis was present in...
the oral cavity. To find the primary focus; a rigorous investigation was realised. So, that, chest radiograph HRCT and a routine medical consultation were requested, but no other focus, except the oral cavity was found. Moreover, a whole body bone scan and SPECT/CT showed an increased activity in the right part of the mandibula and maxilla, presumptive primary infection focus might be the oral cavity. An inflammatory focus, adjacent to tooth or teeth extraction sites has also been reported (Selimoglu et al., 1995; Lo Bello et al., 1984).

Also, before the tuberculin testing of dairy herds, many cases arose from the consumption of milk infected with Mycobacterium bovis. However, in those areas of the world where unpasteurised milk is consumed, bovine tubercule bacilli often cause human infection (Pande et al., 1995; Antico, 1995). Our patient lives in a rustic area where the consumption of unboiled or raw milk is common and, presumably he had consumed milk. Probably, until now, a report on an adult patient with CRF who developed primary oral TBC infection, who did not receive immunosuppressive therapy and who showed all the clinical properties of the disease, and almost using all the diagnostic tests, and showing all the properties such as cord factor of the M. bacterium tuberculosis has not been published in the literature. Also, practitioners need to be aware of the precautions necessary in treating patients. An early diagnosis with prompt treatment will usually result in a complete cure. A major concern for dentists and other health care workers, in the light of reemergence of the disease, is the risk of transmission of TBC in the dental setting. Dentists are involved in the effort to control TBC through early detection and the referral of patients to physicians for proper treatment and by developing and implementing appropriate infection control programs. Indeed, there is still a big gap separating dentistry and medicine. Periodontal evaluation should be performed as part of a medical assessment. The oral health maintenance program for patients receiving dialysis should be reinforced by the dialysis team and dentists.

CONCLUSION

Physicians and dental practitioners are urged to include TBC in the differential diagnosis of persistent lesions of the oral mucosa that is non-responsive to routine cultures and therapy, especially unusual manifestations. The standard treatment is drug therapy that includes a combination of different antibiotics over several weeks. A complete microbiological investigation and biopsy should be carried out and the patient should be subjected to radiographic and laboratory tests. Also, the presumptive identification of M. tuberculosis using the macroscopic evaluation of colonies combined with cords, a virulence factor detection under microscopy is a simple, rapid and inexpensive test. It is recommended that the combined screening test to rapidly identify M. tuberculosis should be carried out in resource-poor settings and in less well-equipped laboratories while awaiting a definite identification by molecular or biochemical methods.

This report emphasizes the importance of early diagnosis aided by histopathological and bacteriological tests. And also, it demonstrates that primary oral TBC is not restricted to adolescents. Early diagnosis and prompt treatment are considered imperative in controlling the spread of this lethal disease in dental and medical settings.

REFERENCES