



Actinomycotic Osteomyelitis of the Maxilla in a Patient on Phenytoin

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ABSTRACT

Actinomycosis is caused by *Actinomyces* species and is relatively rare in humans. Because of the special collateral blood flow, osteomyelitis is less common in the maxilla than the mandible. Although there are few case reports for jaw osteomyelitis, actinomycotic osteomyelitis associated with phenytoin therapy has not been reported before. The data show that antiepileptic drugs induce suppression of the immune system. This report presents a rare case of a 58-year-old man on phenytoin with actinomycotic osteomyelitis, and reviews the relevant literature.

Keywords: *Actinomyces*; Osteomyelitis; Maxilla; Phenytoin; Immune System

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INTRODUCTION

Osteomyelitis refers to inflammation of osseous tissue, which starts as an infection in the calcified part of the bone in the medullary area and quickly spreads to the Haversian system and periosteum [1-4]. It is often caused by *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Escherichia Coli* [1]. The pathogens cause pus formation and edema in the medullary cavity followed by an increase in the intramedullary pressure, leading to vascular collapse through stasis, thrombosis, or ischemia. As a result, bone necrosis and ultimately sequester formation occur as the classic symptoms of osteomyelitis [1].

Osteomyelitis is less prevalent in the maxilla due to its collateral blood flow system and subsequently higher oxygen supply [2,3].

Furthermore, thin cortical bone, bone marrow spaces, and the porosities in the maxilla make it less prone to infection [3-5]. Osteomyelitis is more common in young adults and women than men (2:1 ratio) [6]. Facial osteomyelitis is rare [7]. Osteomyelitis was a common disease with a high mortality rate before the advent of antibiotics [4,5].

The causes of infection in osteomyelitis can be traumatic, rhinogenic, or odontogenic. Contributing factors include diseases that have weakened the immune system, such as diabetes mellitus, HIV, malnutrition, or use of chemo-therapeutic agents and other immunosuppressive drugs [5].

Actinomycosis is an endogenous saprophytic infection that is relatively uncommon in humans [5], and is very rare in the oral mucosa

[7]. *Actinomyces* found in nature are unable to cause diseases in humans [6]. The prevalence of jaw actinomycosis infection is low in the mandible (6.53%), buccal mucosa (4.16%), chin (3.13%), maxilla (7.5%), and temporomandibular joint (0.3%) [3].

Actinomycotic osteomyelitis is the spread of *Actinomyces* to the alveolar bone and does not have a clear pathological mechanism [8]. To induce disease, *Actinomyces* should first penetrate into the tissue, and then, they need a perfect environment for growth and proliferation. Dental lesions, loss of tissue viability due to trauma and necrotic bone can be considered as favorable environments for this pathogen [6]. This report presents a rare case of a 58-year-old man on phenytoin with actinomycotic osteomyelitis, and reviews the relevant literature.

CASE REPORT

A 58-year-old man complaining of sudden loss of his upper left premolar presented to our department. He had no apparent problems but upon waking up he found the tooth in his mouth with no pain or bleeding. Clinical examination indicated other missing teeth near the lost tooth. The upper left second premolar had grade 3- and the upper left canine had grade 2-mobility.

The socket of the lost tooth was completely empty, and there was a mass in the form of an erythematous nodule with medium consistency on the buccal edge of the socket, which was not painful or hemorrhagic. His other teeth appeared to be sound without any mobility. The patient underwent periapical radiography of the maxillary left teeth from the lateral incisor to the second premolar. A unilateral periodontal ligament widening was observed distal to the maxillary second premolar (Fig. 1). Considering the sudden tooth loss and unilateral periodontal ligament widening, malignancy was suspected. We performed a biopsy from the erythematous nodule, that showed chronic diffuse inflammation. The patient was discharged afterwards, but was followed and recalled due to the suspected history.

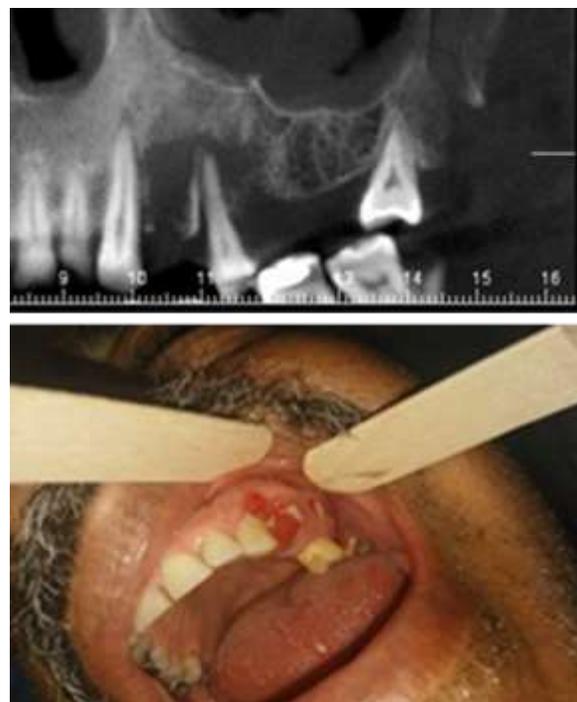


Fig. 1: Unilateral periodontal ligament widening in the cropped view of OPG. Loss of teeth around the fallen tooth and a mass in the form of an erythematous nodules

Three weeks later, the patient mentioned in a telephone conversation that a large mass had emerged in the area of the missing tooth. The patient was scheduled an emergency appointment.

On clinical examination, a buccopalatally expanded firm mass, which had filled the extraction socket was found. There was no bleeding or pain on palpation. Cone-beam computed tomography was requested which revealed a radiolucent lesion with a moth-eaten border in the left side of the maxilla, extending from the distal of the maxillary left canine to the edentulous molar area, limited to the alveolar process. The sinus floor and the basal bone appeared to be intact.

There was unilateral widening of the periodontal ligament with asymmetric destruction of the lamina dura and no root resorption. The lesion had destroyed the buccal plate (Fig. 2). The differential diagnosis included 1) intra-osseous squamous cell carcinoma, and 2) osteosarcoma (lytic phase).

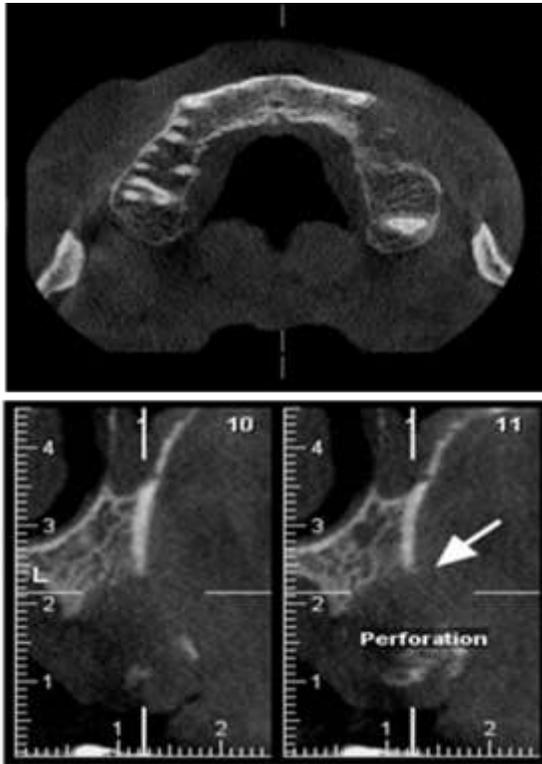


Fig. 2: Perforation of the buccal and lingual cortical plates on cropped view of cone-beam computed tomography scan

The second incisional biopsy was obtained from the mass inside the socket that was facing outwards. Pathologic analysis of hematoxylin/eosin-stained sections (Fig. 3) revealed fragments of necrotic bone trabeculae enclosing large colonies of actinomycotic organism. The bone trabeculae showed a loss of the osteocytes from their lacunae and prominent reversal lines. Intertrabecular spaces were filled with necrotic debris and an acute inflammatory infiltrate consisting of poly-morphonuclear leukocytes and large microbial colonies. In the overlying oral mucosa, dense lymphoplasmacytic infiltration, marked exocytosis, and spongiosis were notable. The buccal cortical plate at the site of the maxillary left second premolar was isolated and sent for pathological assessment of the second biopsy. The report was very surprising because osteomyelitis required a systemic or localized condition as a risk factor, and it rarely occurs in the maxilla, and actinomycotic osteomyelitis is even rarer.

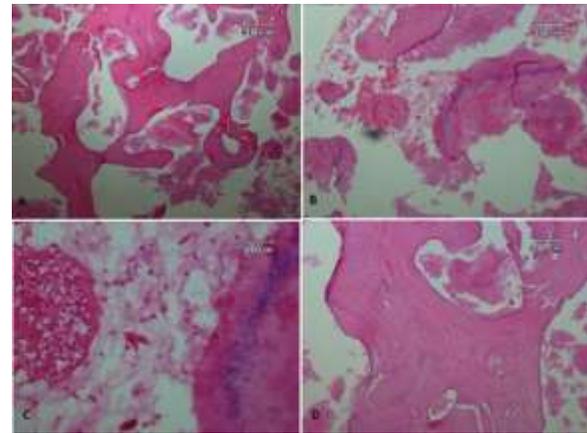


Fig. 3: H&E-stained section showing (A) necrotic bone trabeculae enclosing large colonies of actinomycotic organism ($\times 40$). (B) Characteristic feature of an actinomycotic colony with basophilic core and eosinophilic peripheral portion ($\times 40$). (C) Polymorphonuclear leucocytes surrounding actinomycotic colonies ($\times 400$). (D) Necrotic thickened bone trabeculae with sclerosis and prominent reversal lines that exhibit loss of osteocytes from their lacunae ($\times 100$)

Therefore, the subject received a complete work-up to detect local and systemic factors. The patient had been taking phenytoin for 14 years due to epilepsy, which had shown significant improvement during the past 8 years with no recurrence of seizures. However, a full examination was requested for further reassurance despite the fact that he had no history. Complete blood count and electrolytes were normal. Only HDL was slightly above the normal range of 30-60mg/dL (72mg/dL). Full debridement was performed to reach sound bone tissue, and the area was washed and sutured and amoxiclav was prescribed every 12h for 2 weeks. The patient has been followed for 10 months with no problems so far. Since his clinical symptoms were not consistent with the disease, osteomyelitis was not initially considered as the most likely diagnosis; but the patient was properly tested and followed, eventually leading to the correct diagnosis and management. While receiving treatment, the patient was referred to his physician to change his medication because otherwise, he might not respond well to treatment.

The patient is still routinely controlled and is in good general health.

Literature Review

Relevant databases were searched from 1960-2020 and 22, 11, 128, 2 and 5 articles were retrieved from Google Scholar, PubMed, ClinicalKey, ScienceDirect and Scopus, respectively.

After omitting repetitions, mandibular cases, and reports of osteomyelitis without actinomycosis, we found 11 articles that presented 13 cases (Table 1) [3,6,7,9-16], of which, only 4 were men [6,9,11,12] and two were in the 5th and 6th decades of life [6,9]. To the best of our knowledge, this is the first time that phenytoin has been proposed as a risk factor for this condition.

Table 1: Overview of patients with underlying diseases, and age and gender of patients with lesions in maxilla

Year	Author	Gender	Age	Underlying Disease
2019	Agarwal et al, [9]	Male	52	Diabetics with poor control
2019	Bano and Parveen [10]	Female	61	Chronic diabetes mellitus
2018	de Oliveira et al, [1 ^Δ]	Female	76	Chronic diabetes mellitus/ Hypertension
2018	Baldawa et al, [11]	Male	18	Habit of chewing tobacco
2016	Meethal et al, [7]	Female	79	Chronic diabetes mellitus
2015	Gannepalli et al, [3]	Female	50	Tooth extraction
2011	Garg et al, [12]	Male	42	Tooth extraction
2017	Sezer et al, [14]	Female	37	Root canal treatment
2017	Sezer et al, [14]	Female	67	Tooth pulling
2017	Sezer et al, [14]	Female	60	Root canal treatment
2000	Yamada et al, [13]	Female	50	Healthy
1974	Stenhouse and Mac Donald [6]	Male	61	Healthy
1966	Hovi et al, [16]	Child	Child	Aplastic anemia

DISCUSSION

Osteomyelitis is relatively uncommon in the jaws [9]. *Actinomyces israelii* is the main cause of neck and face actinomycosis. This pathogen is normally found in decayed teeth, dental plaque, gingival grooves, and tonsillar crypts [6,7,14]. Therefore, poor oral hygiene, unhealed sockets, and surgical manipulation can facilitate its penetration into deeper tissues [3]. In general, the infection can be primary or secondary to nonspecific local osteomyelitis [14].

Actinomyces lack the hyaluronidase enzyme that is responsible for degradation of tissues [14]. Hence, it has low virulence and invasiveness, but other bacteria may act as co-pathogens and facilitate the development of infection by this microorganism through its toxins and enzymes. The microbial flora plays a synergistic role meaning that it creates a specific ecosystem in which there is potential for oxygen reduction, facilitating the proliferation of anaerobes.

Following the development of an anaerobic environment, the oxygenated environment with high vascular supply is destroyed and replaced by a very irregular granular tissue (sulfur granules) that in turn causes further growth of anaerobic microorganisms. In fact, the infection manifests as a granulomatous inflammation that comes with a purulent necrotic core characterized by the accumulation of bacterial filaments surrounded by neutrophils. Instead of complete lytic destruction of bone, granulomatous inflammation results in formation of bone spicules, leading to the development of sclerosis which resembles bone tumors [3,17]. Due to its diverse clinical picture in the head and neck, it can resemble a benign infection or a metastatic tumor [7]. Actinomycosis may look like fungal infections. Thus, it is usually discussed in mycology, while *Actinomyces* are in fact filamentous and prokaryotic Gram-positive bacteria [14,17]. Actinomycotic osteomyelitis is rare in the

maxilla due to its excellent blood supply and thin bone structure. Infectious maxillary sinusitis [14], an unhealed extraction socket, hyperglycemia [4], and immunosuppression caused by chemotherapy [16], can be predisposing factors for maxillary osteomyelitis. Non-healing wounds after the long-term habitual use of chewing tobacco should be distinguished from actinomycotic osteomyelitis [11]. Our patient had none of the above-mentioned symptoms or disorders.

Actinomycotic osteomyelitis has manifestations such as paresthesia, exposure of bone, pathologic fracture of bones, and persistent infection after root canal treatment and tooth extraction, with no history of trauma [14]. In our case, the patient had no symptoms like pus, fistula, swelling, or sensory disturbances. In addition, there was no history of trauma to the jaws or to the head and face.

The diagnosis of actinomycotic osteomyelitis is often based on clinical, radiographic, and microscopic findings [7]. Clinically the disease can be painless or painful and mimic different benign or malignant conditions. Culturing this microorganism is technically difficult because it requires an anaerobic environment [7,14]. Use of polymerase chain reaction is expensive [3] and serological methods are not reliable, especially for those with immunodeficiency [16]. Biopsy and histopathological examination are strongly recommended for diagnosis [3,14,16], which were used for the final diagnosis in our patient.

Imaging techniques are also available for advanced assessment of osteomyelitis. Computed tomography is the best modality for assessment of the calcified structures especially the cortical plate. The isotope ^{99m}Tc and bone scan of methylene diphosphonate is another modality, which can help detect the acute involvement, but they cannot be used for definite diagnosis due to poor resolution. Positron emission tomography was recently found suitable to differentiate between normal and damaged bone [4]. Our patient was first examined based on his panoramic radiograph, and then cone-beam computed tomography was requested for further evaluation.

The treatment of osteomyelitis may vary from non-invasive approaches to more aggressive radical treatments. A combination of high-dose antibiotic therapy along with surgery is often effective. Surgical treatment includes removal of sequestrs and mobile teeth and debridement of the area to achieve healthy bleeding tissue, and decortication, resection and reconstruction [3,5]. Since under in vitro conditions, *Eikenella* and *Actinomyces* within the sulfur granules escape from direct contact with antibiotics and leukocytes, surgery along with antibiotic therapy is considered as the basis of treatment. [3,17]. In cases with poor response to antibiotic therapy and surgery, the treatment may continue with amphotericin B [16]. Our patient also underwent debridement surgery, and received antibiotics and was followed for 10 months with no problem.

According to the literature, antiepileptic drugs like phenytoin, valproic acid, and carbamazepine affect the cytokine levels. Thus, their intake increases the level of IL1 β , IL2, IL5, IL6T and TNF α [18]. Also, they decrease the number of T cell suppressors [19], and increase the ratio of T-helper₁ to T-helper₂ [20]. Phenytoin intake can decrease lymphoid cells [21]. Various studies have found that phenytoin suppresses the immune system [18,22] and it may even cause lymphoma in the presence of other factors [21]. Therefore, occurrence of actinomycotic osteomyelitis in our patient might be due to many years of phenytoin intake. Our literature review from 1960-2020 revealed that this case was rare not only because of its maxillary location, but also because of the underlying disease (epilepsy). To the best of our knowledge, this is the first case of actinomycotic osteomyelitis that may be related to long-term use of phenytoin. It is noteworthy that the present report is the only one reporting actinomycotic osteomyelitis in a male patient.

CONCLUSION

Actinomycotic osteomyelitis is a rare infection, especially in the maxilla. Chemotherapy, diabetes mellitus, and other

immune-suppressive conditions can increase its prevalence. Epileptic drugs like phenytoin affect the level of cytokines and decrease the number of T-cell suppressors. To the best of our knowledge, our case was the first male patient with actinomycotic osteomyelitis of the maxilla, for whom long-term use of phenytoin was hypothesized to be the predisposing factor.

CONFLICT OF INTEREST STATEMENT

None declared.

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