

# TAMOXIFEN AS A POSSIBLE CAUSE OF JAW OSTEONECROSIS

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### ABSTRACT

**Objectives:** Medication-related osteonecrosis of the jaw (MRONJ), an oral complication manifested by exposed jaw bone, attracts scientific attention, especially for its etiology and therapy. The majority of reported cases are related to antiresorptive and antiangiogenic drugs. However, other medications such as tamoxifen can cause MRONJ as well. This case study highlights that the use of tamoxifen could lead to osteonecrotic changes in the jaw bone.

**Case report:** We presented a case of a breast cancer patient with necrotic jaw changes after single tooth extraction. The patient was using tamoxifen, a selective estrogen receptor modulator. Exposed necrotic bone persisted for more than eight weeks. The patient experienced severe pain. Bone sequestrectomy using a piezo device was performed. The remaining bone was covered with platelet-rich fibrin (PRF) membrane, and the wound was primarily sutured. The postoperative period was uneventful. The lesion was monitored radiologically and clinically. The wound healed completely.

**Conclusion:** Clinicians must be aware of the possibility that tamoxifen can be related to osteonecrotic jaw changes after tooth extraction. PRF was a good treatment option in the presented case.

**Key words:** Osteonecrosis of the Jaw; Tamoxifen; Tooth Extraction; Platelet-rich Fibrin (PRF)

## Introduction

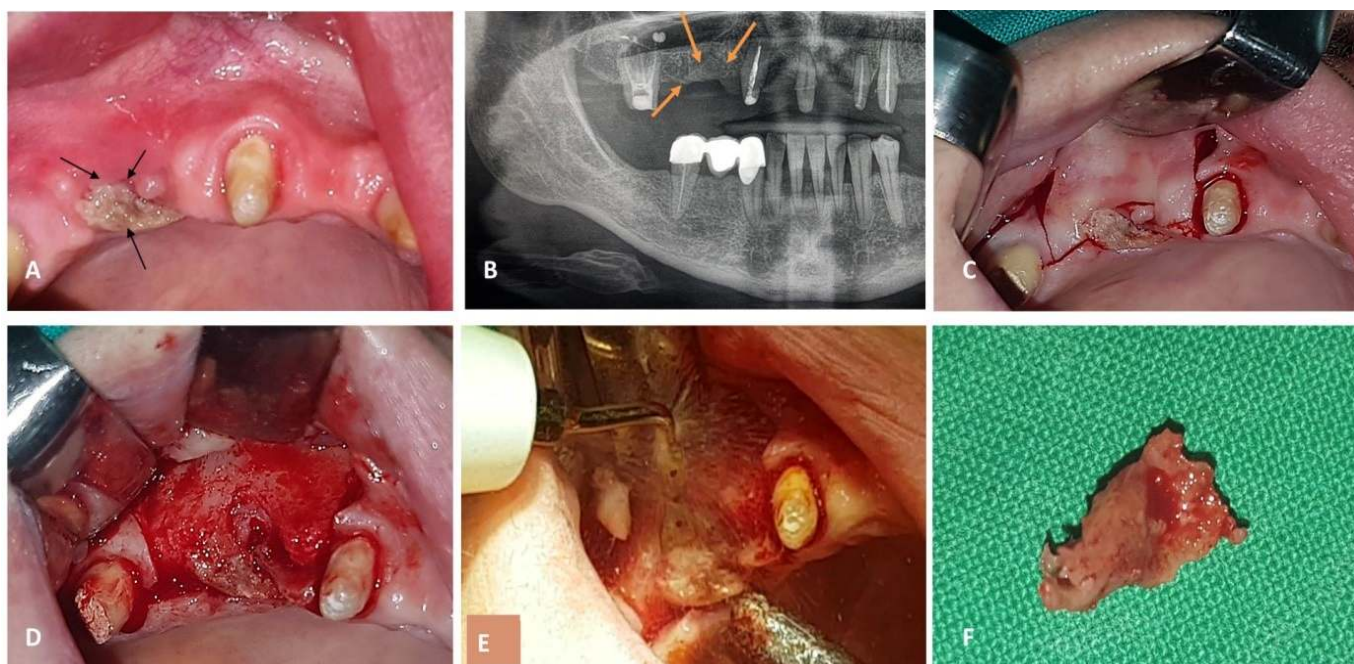
Osteonecrosis of the jaw is defined as the loss of the bone matrix of the jaw bone. The cause of osteonecrotic changes can be related to the use of certain medication causing changes in the bone microstructure. These medicaments are characterized by quick disposal and accumulation in the bones. They inhibit angiogenesis, i.e., prevent the formation of new blood vessels. The cause of osteomyelitis after bone necrosis can be a local infection, invasive dental procedures and the patient's general health condition [1, 2]. The most significant risk for the occurrence of osteomyelitis of the necrotic bone exists if oral surgical procedures were done [2]. Osteonecrosis of the jaw is mostly found in women aged 55-68 diagnosed with breast cancer or osteoporosis [5]. Osteonecrosis usually affects the jawbones, as they are susceptible to active remodeling [2]. The mandible is more often affected than the maxilla. Drugs known to cause osteonecrotic changes in jaws are from a group of antiresorptive and antiangiogenic drugs. The first case was reported

in 2003, and it described a case of osteonecrosis of the jaw caused by antiresorptive drugs - bisphosphonates [3]. However, the list of medicines that may cause this condition expanded, and now we know that other medications such as denosumab, bevacizumab, sunitinib, corticosteroids, immunomodulators, and others can cause osteonecrosis as well [1]. Osteonecrosis of the jaw caused by these medications is called *Medication-related osteonecrosis of the jaw* - MRONJ.

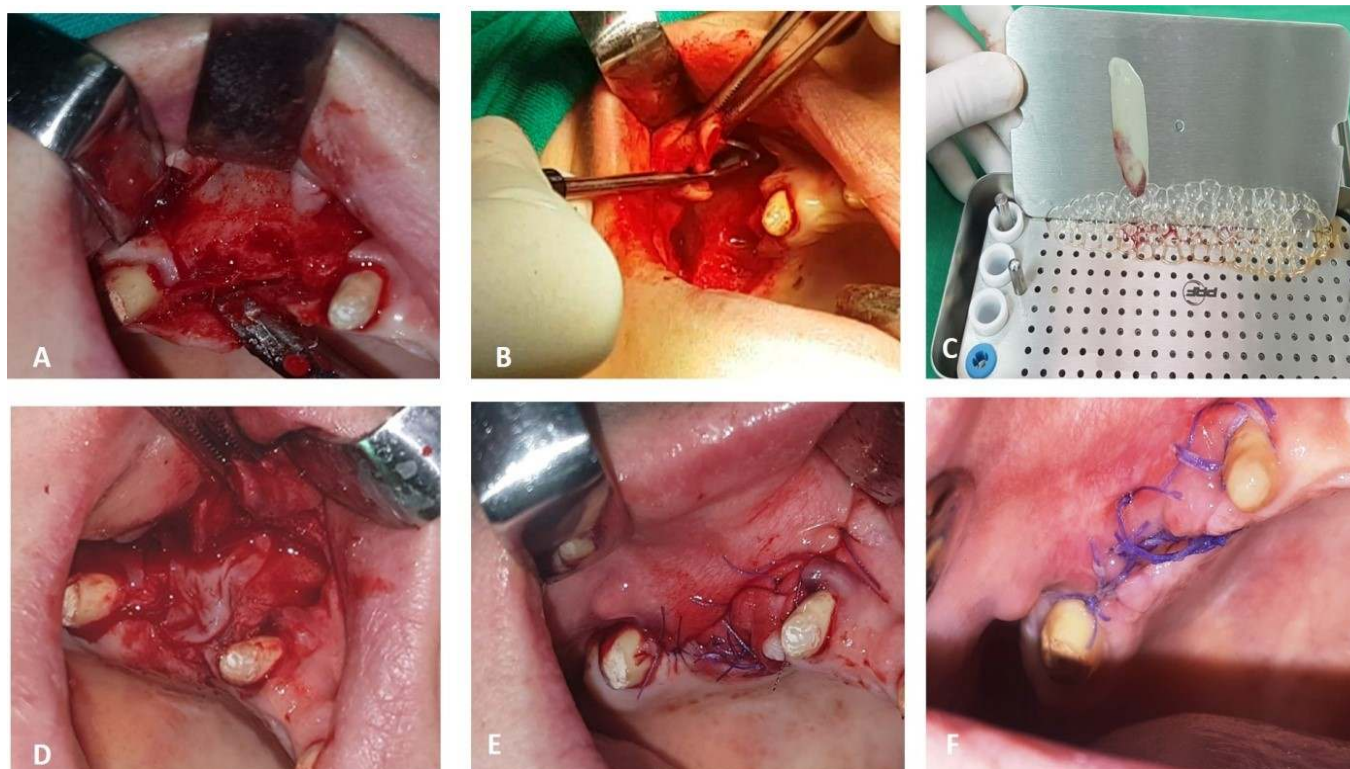
MRONJ is clinically manifested in the form of exposed bone, which is present in 94% of cases [6]. Alongside, pain, tooth mobility, ulcers, extraoral fistulae, and symptoms of infection can be present. In the advanced stage of the disease, local infection with a general inflammatory response can occur as well as pathological fractures of the jaw [11].

The diagnosis of MRONJ is based on several criteria: antiresorptive or antiangiogenic drug use in the patient's medical history, clinical exposure of the bone site for more than eight weeks, and no radiotherapy or metastasis in the jaw bone [1].

We aimed to show the therapeutic approach to tamoxifen caused osteonecrosis of the upper jaw following tooth extraction.



**Figure 1.** A - An exposed necrotic bone on the right side in the upper jaw;  
 B - Panoramic X-ray view - osteonecrosis of the jaw in the upper right lateral segment;  
 C - Incision; D - Elevated mucoperiosteal flap allows insight into the condition of the bone;  
 E - Removal of the necrotic part of the bone with a piezzo; F - Removed part of the bone



**Figure 2.** A - The surgical wound after removing bone sequestrum;  
 B - Flap elongation with the 'brushing' technique; C - PRF membrane;  
 D - Application of the PRF membrane into the bone defect; E - Sutures;  
 F - Operative site on the 7<sup>th</sup> postoperative day.

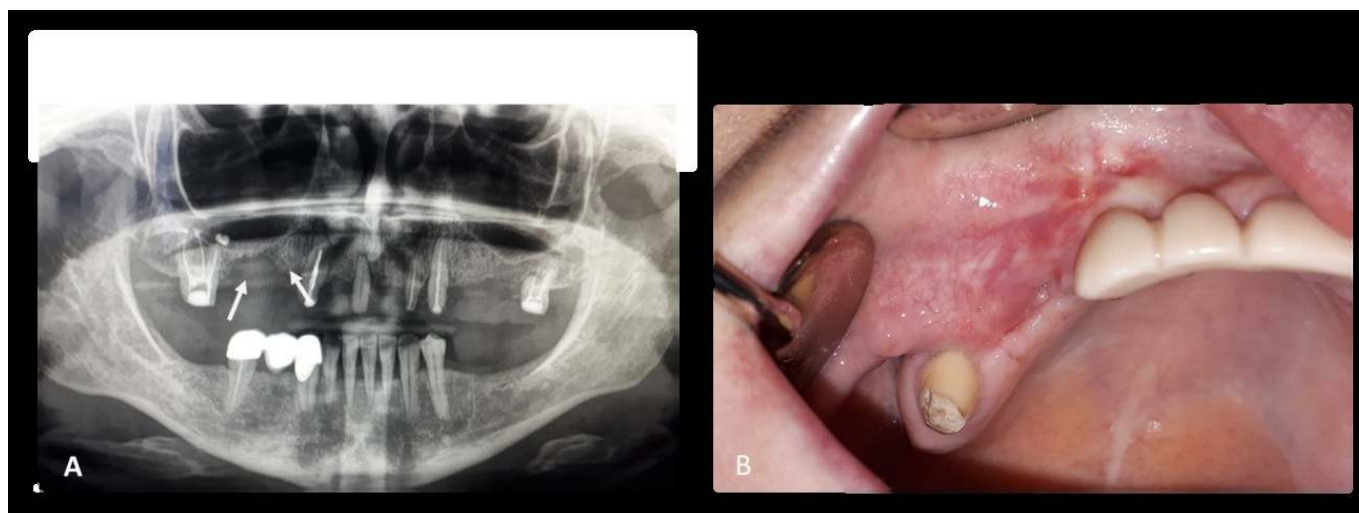
## Patient's Presentation

A 46-years old woman was referred to the Department of Oral Surgery due to pain and prolonged wound healing. She was a breast cancer patient treated with tamoxifen (Nolvadex<sup>®</sup>, AstraZeneca) that had her tooth 15 extracted, after which the wound did not heal. The tooth was removed three months before her visit. Clinical intraoral examination revealed exposed necrotic bone that persisted for more than eight weeks.

The redness and swelling of soft tissues were notable; ulceration was not present (**Figure 1. A**). The patient did not notice any bleeding at the exposed site. Panoramic X-ray showed necrotic bone changes in the region of the tooth 15 (**Figure 1. B**). Based on the history of tamoxifen consumption and exposed necrotic bone that persisted more than eight weeks, a diagnosis of the MRONJ was made.

The patient was prescribed antibiotic treatment (2g of Amoxicillin per day) and scheduled for the sequestrectomy procedure. The treatment was done in the operating ward under sterile conditions. Infiltration anesthesia in the area of teeth 15-16 was applied, trapezoid incision in the region of tooth 13 – 15 was made, and a full-thickness flap was elevated (**Figures 1. C, D**). With the help of piezoelectric bone surgery, necrotic bone was removed, and sharp bone edges were smoothed (**Figure 1. E**). The removed bone sequestrum was sent for histopathological examination (**Figure 1. F**).

The surgical field was rinsed abundantly with NaOCl (sodium hypochlorite 0.03%), and the PRF membrane was applied in and over the defect (**Figure 2. C, D**). The wound was primarily closed with resorptive sutures using the apical mattress technique to ensure healing without tension (**Figure 2. E**). She was prescribed antibiotics (2g of



**Figure 3.**

A - Panoramic X-ray 1 month after the procedure; B - Successful wound healing can be noticed eight weeks postoperatively.

Amoxicillin per day) for 10 days. The patient was monitored radiologically and clinically through periodical follow-ups (**Figure 3.**).

The histopathologic analysis showed empty osteocyte lacunae within the preserved bony trabeculae. Inflammatory cells and bacteria were present with the necrotic bone. Histopathologic findings confirmed the diagnosis of MRONJ in stage one.

Panoramic X-ray 1 month postoperatively showed bone cavity filled with soft tissue (**Figure 3. A**). At the 3-month follow-up, successful soft tissue healing could be observed (**Figure 3. B**).

## Discussion

Osteonecrosis of the jaw is a very severe side-effect of certain medications that are used to treat osteo metabolic or malignant diseases. It was first noticed in 2003 by oral and maxillofacial surgeons, who detected this change in oncologic patients and described it as extraction wounds that do not heal [4].

There are several stages of MRONJ. It starts with prolonged healing of the extraction wound accompanied by pain and swelling of soft tissues. The second phase is reflected in the presence of ulcerous changes of the exposed jaw bone, extraoral fistulas and tooth loss. A more severe

clinical picture is presented when osteonecrotic changes are accompanied by a pathological fracture of the jaw bones and paresthesia of the lower lip [4,7].

Since the results of MRONJ therapy are often limited, the treatment requires a serious approach. Pain treating is considered imperative in the treatment of osteonecrosis. Three methods of treatment of MRONJ are described in the literature: conservative, surgical and supplemental. The conservative method includes rinsing the oral cavity with an antibacterial solution such as a 0.12% solution of chlorhexidine, and the use of antibiotics - penicillin or clindamycin combined with metronidazole and antifungal therapy [8].

The surgical method involves surgical debridement, sequestrectomy, tooth extraction with removal of osteonecrotic bone, bone resection and reconstructive surgery. Necrotic bone fragments are usually removed surgically by sequestrectomy [8]. Bone defects occurring after removing the necrotic bone fragment can be repaired in many ways. One of the novel approaches is using PRF - an autologous transplant obtained from the patient's blood [9]. PRF, as a biomaterial that can enhance tissue regeneration and reduce postoperative complications, has proven to be effective in closing bone defects and soft tissue regeneration in patients with MRONJ. [10]

Supplemental therapy which includes ozone therapy, lasers, PRF application, mesenchymal stem cell therapy can be combined with conservative and surgical therapy for better results [8].

Many studies underline that medicines from a group of antiresorptive and antiangiogenic drugs can cause osteonecrotic changes in jaw bones [11]. This report focuses on tamoxifen and its possible effect on development of jaw osteonecrosis in a breast cancer patient after tooth extraction. Tamoxifen is a competitive partial agonist of estrogen receptors. The drug is prescribed as adjuvant therapy in patients with estrogen receptor-positive breast cancer, but also as a preventive therapy in high-risk patients [14].

Contemporary literature lists tamoxifen as a drug that could affect the development of osteonecrosis. From January 2004 to November 2012, 744 patients using tamoxifen were reported with osteonecrotic jaw bone changes by FDA [12]. Tamoxifen can have both positive and negative effects on the bone [14]. It increases bone mineral density in postmenopausal women while it reduces bone density in women of premenopausal age [12, 13]. However, the connection between selective estrogen receptor modulators and osteonecrosis is not quite understandable. In their review, King and associates pointed out that only one patient receiving raloxifene was reported with osteonecrosis [15,16]. It remains to be seen whether the future will show more cases of osteonecrosis caused exclusively by tamoxifen.

Our patient was an oncologic, premenopausal woman that was prescribed tamoxifen as a part of breast cancer therapy. Therefore, she was in a high-risk category for developing osteonecrosis. All this data, combined with the presence of an extraction socket that did not heal for eight weeks, led us to the diagnosis of MRONJ.

It is evident now that osteonecrosis of the jaw can be caused by a spectrum of medications mostly used in oncology patients that directly or secondly affect bone metabolism. Alongside we are witnessing an increased incidence of cancer patients worldwide, many of which at some point

need dental treatment. Therefore raising awareness of MRONJ and a multidisciplinary approach to this problem of both medical and dental specialists would contribute significantly to the prevention of MRONJ.

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