Osteonecrosis of the Jaw in a Crohn's Disease Patient following Infliximab Therapy: A Case Report and Literature Review

Andreas Sakkas*, Sebastian Heil, Steffen Kargus, Oliver Thiele and Robert Mischkowski

Department of Oral, Maxillofacial and Facial Plastic Surgery, Klinikum Ludwigshafen (Hospital), Ludwigshafen, Germany

Abstract: ***Introduction:*** Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication, occurring to patients undergoing treatment with antiresorptive medication, such as bisphosphonates, denosumab or bevacizumab, for different oncologic and non-oncologic diseases. The aim of this study is to report a case of MRONJ in a young patient treated with infliximab, a tumor necrosis factor-a inhibitor used in the treatment of immune-mediated inflammatory diseases such Crohn's disease, ulcerative colitis, ankylosing spondylitis, rheumatoid and psoriatic arthritis. ***Case Report:*** A 27-year-old female patient diagnosed with Crohn's disease, who had been undergoing intravenous infliximab therapy every seven weeks for 8 years, sought our oral and plastic maxillofacial department with a peri-mandibular abscess for further treatment. The patient underwent surgical treatment, including the extraoral sub-mandibular incision of the abscess and the extraction of the lower second premolar under the administration of intravenous antibiotics. We traced a wound dehiscence and delayed healing procedure of the extraction's alveolar bone, and five weeks later, the patient returned with an abscess recurrence around the mandibular angle area. The patient underwent surgical treatment with wide bone resection and debridement of the necrotic tissues. After follow-up (4 months), the patient completely healed without signs of recurrence. ***Discussion:*** Osteomyelitis of the jaw by patients treated with infliximab has been sparsely described in publications. This case confirms the potential role of infliximab in the pathogenesis of MRONJ. Since the pathomechanism of MRONJ under infliximab therapy remains unclear, we recommend a regular oral check-up before starting therapy, as well as during the therapy with infliximab, in order to possibly prevent the MRONJ onset.

Keywords: Medication-Related Osteonecrosis of the Jaw, Infliximab, TNF-a Inhibitors, Crohn's Disease and Osteomyelitis.

INTRODUCTION

In 2014, a special committee of AAOMS recommended the change in nomenclature for BRONJ to MRONJ due to the growing number of osteonecrosis cases associated with other antiresorptive and antiangiogenic drugs [1,2]. In 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) also defined the medication-related osteonecrosis of the jaw (MRONJ) as "the presence of exposed necrotic bone or bone that can be probed through an intraoral or extra-oral fistula in the maxillofacial region, that has persisted for longer than eight weeks, occurring in patients undergoing treatment with antiresorptive or antiangiogenic agents with no history of radiation therapy or obvious metastatic disease to the jaws" [1]. The clinical manifestation of MRONJ is multifactorial, mainly depending on the duration of antiresorptive therapy, oral or intravenous application, combined treatment with corticosteroids or diverse chemotherapies and local risk factors such the gravity of tissue trauma caused by surgery and oral health of the patient [3,4].

The role of antiresorptives such as denosumab, bevacizumab, rituximab, adalimumab and sunitinib in the pathomechanism of MRONJ has been already described in several publications [2,5-20]. Since the receptor activator of nuclear factor kappa-B ligand (RANKL) and TNF-a share some biological features and RANKL inhibition by denosumab is associated with MRONJ, TNF-a inhibition may also be associated with MRONJ [2].

Infliximab is a chimeric human-murine IgG1 monoclonal antibody that acts as a tumor necrosis factor-α (TNF-α) inhibitor. TNF-a is an important cytokine involved in the pathogenesis of chronic immune-mediated inflammatory diseases. The treatment of rheumatoid arthritis, adult and pediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis appear as possible indications for infliximab. Neutralizing TNF-a with the use of TNF-a inhibitors reduces disease activity in these autoimmune diseases [11,12].

Previous reports have suggested a possible association of TNF-a inhibitors, used in the treatment of immune-mediated inflammatory diseases and medication-related osteonecrosis of the jaw (MRONJ). However, the sparse number of these clinical reports to date could not allow a reliable assessment of the frequency and severity of MRONJ caused by TNF-a inhibitors [13-16].

In the international literature, two case reports and one cohort study have already described the clinical occurrence of MRON by patients treated with infliximab [15,17,18]. In our clinical case we depict a case of extensive osteonecrosis of the jaw in a patient affected by Crohn's disease who underwent oral surgery and who had been administered infliximab therapy for several years. Since a comprehensive assessment of MRONJ in patients treated with TNF-a inhibitors has not been performed to date, this paper aims to have infliximab considered and added to the list as a common TNF-a inhibitor medication causing MRONJ.

CASE REPORT

A 27-year-old female patient was referred to our clinic of Cranio-Maxillo-Facial Surgery (Klinikum Ludwigshafen in Germany) in September 2019 for the emergency treatment of an extended peri mandibular swelling on the right mandibular side.

The patient's general medical history revealed that she had been diagnosed with Crohn's disease in 2011 and, therefore, infliximab (250 mg intravenous infusion every 7 weeks) and oral prednisolone were administered. Other predisposing risk factors were poor oral health and smoking. The patient had never undergone antiresorptive or antiangiogenic therapies in the past.

*Address correspondence to this author at the Department of Oral, Maxillofacial and Facial Plastic Surgery, Klinikum Ludwigshafen (Hospital), Ludwigshafen, Germany; Email: ansakkas@yahoo.com; Tel: +49-621-503-37244; Fax: 0621 / 503 - 3709

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The patient was referred to our clinic due to pain impairment and increasing mandibular swelling over 3 days. The extraoral clinical examination highlighted a peri mandibular abscess extended from the mental area to the right mandible angle without skin ulceration or secretion. Additionally, the disorder of the swallow function and a reduced painful mouth opening of about 1 cm were also detected. Intraorally, the lower second right premolar was affected severely periodontal affected presenting mobility grade 2. At the initial orthopantomograph of the patient, an apical radiolucency of the second premolar was detected, as well as a generalized marginal periodontitis combined with tooth loss and horizontal bone loss (Figure 1).

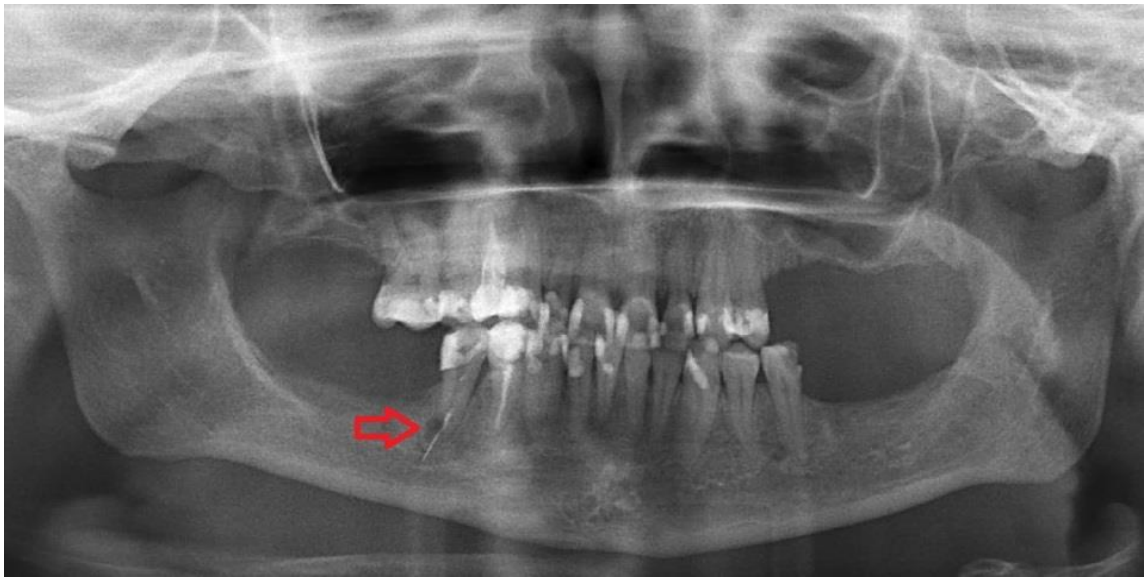
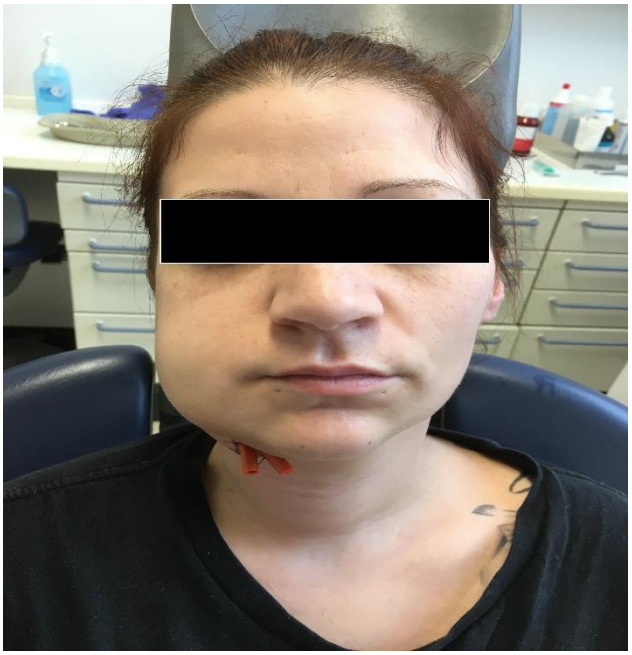


Figure 1: Patient's radiographic feature. Apical radiolucency of the second right lower premolar and generalized periodontal disease including tooth and bone loss.

Subsequently, the patient underwent surgical treatment under general anesthesia, which consisted of extraoral incision and drainage of the perimandibular abscess and the removal of the lower second right premolar (Figure 2A,2B). The intravenous admission of antibiotics with ampicillin/sulbactam 3gr (Unacid®, Pfizer Pharma GmbH, Germany) three times a day and appropriate analgesia was applied for 5 days under hospitalization and continued for 5 days orally. The postoperative orthopantomograph showed the complete removal of the premolar tooth (Figure 3).



A

Figure 2A,B: Clinical feature of the patient after surgical incision in the submandibular area and drainage with 2 silicon tubes sutured at the soft cervical tissues.

During the time of hospital admission, the swelling was treated extraorally with an antiseptic solution (Octenisept®, Schülke & Mayr GmbH, Germany) under continuous antibiotic therapy. After 5 days, the extraoral drainage tubes were removed and the patient was released home after being informed of the daily control appointments in our clinic. A local treatment consisted of irrigating the mouth with chlorhexidine and appropriate mouth hygiene. After the hospital admission, no more antibiotics were administrated. On review, there was a considerable improvement in her physical condition; her systemic symptoms had objectively subsided and the pain reduced, decreasing the analgesic intake. The clinical increase of

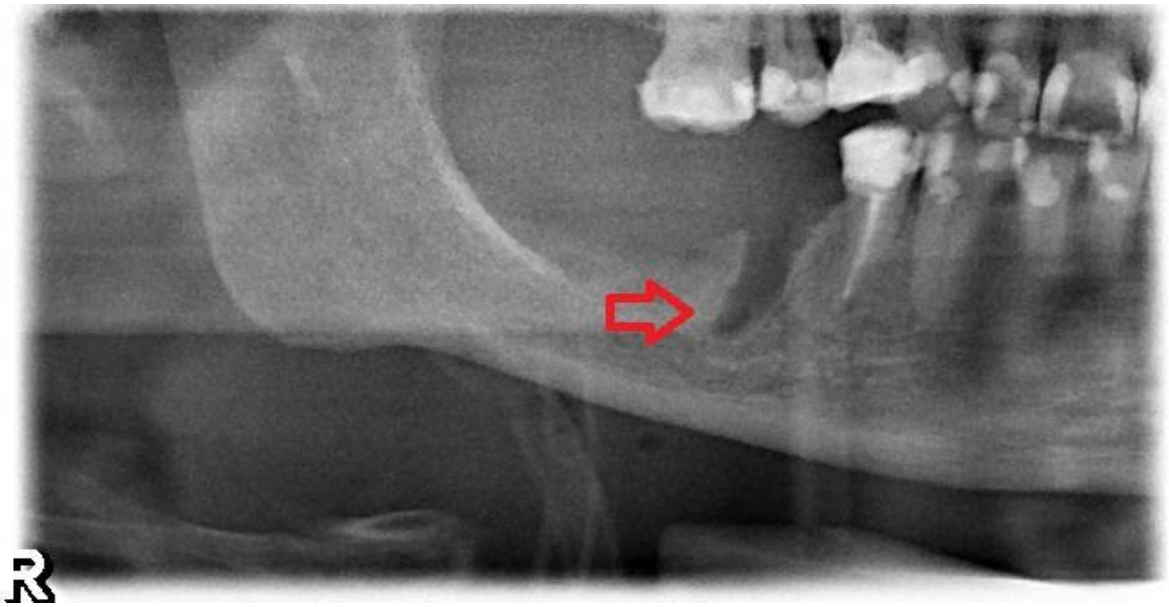


Figure 3: Postoperative orthopantomograph of the surgical side showing the complete tooth removal causing the perimandibular abscess.

the mouth opening was also detected. Two weeks post operation, we noticed a complete remission of the perimandibular swelling, but a permanent intraoral dehiscence of the alveolar bone and an accumulation of food debris at the surgical site. Despite the daily irrigation with chlorhexidine mouth rinse, the intraoral wound healing was uneventful, showing avital alveolar bone exposed without pus secretion (Figure 4). This was treated conservatively with local rinses of a chlorhexidine solution without antibiotics, aiming to reach secondary wound closure without bone debridement. The treatment with infliximab was not interrupted at any time during the treatment in our clinic.

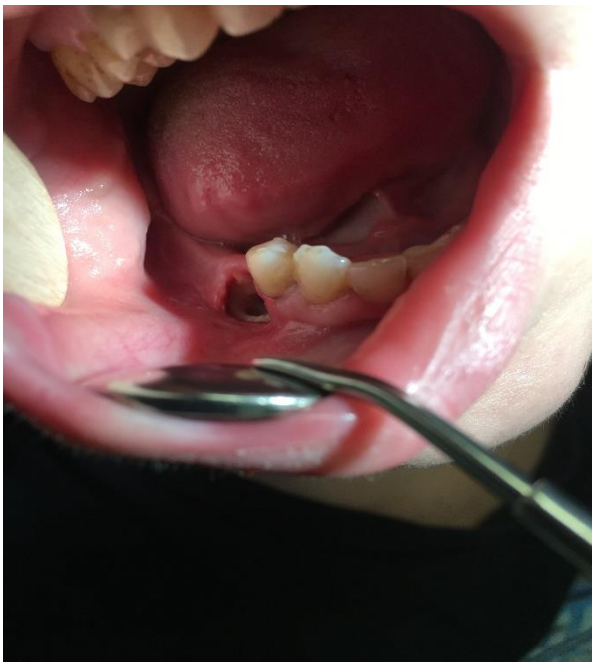


Figure 4: Intraoral necrotic bone exposure on the anterior right mandible of the surgical side. The lesion was classified as stage 3 medication-related osteonecrosis of the jaw according to the American Association of Oral and Maxillofacial Surgeons staging system [1].

Five weeks postoperative, the patient was reviewed as an emergency in our clinic again, with a recurrence of the perimandibular abscess. This time the abscess was extended from the ramus to the mandible angle. The orthopantomograph showed diffuse radiolucency around the extraction´s alveolar bone, which was quite distinct from the direct postoperative radiograph. The radiolucency extended beyond the extraction´s socket more distally to the posterior mandible remarking radiologic signs of mandibular osteomyelitis (Figure 5A). A sagittal view of digital volume tomography at the surgical area showed the loss of bony trabecular architecture and bony lysis with local penetration of the lingual cortical plate (Figure 5B).

The clinical and radiographic examination led to the diagnosis of mandibular osteonecrosis and the patient underwent surgical procedure under general anesthesia, consisting of mandibular partial decortication of the infected bone, involving the residual alveolar process anterior-posterior and the exposed bicortical plate to vital bone, with preservation of the alveolar inferior nerve and the basal cortical margin. After resection, the remaining avital bone surface was treated by a rotating burr and diamond burr to remove residual infected and necrotic tissues, to possibly prevent MRONJ recurrence. The alveolar inferior nerve was exposed intraoperatively and protected from all cutting instruments and devices. The wound closure was performed after periosteal releasing incisions, to achieve a tension free adaption of the soft tissues (Figure 6). The extraoral incision of the abscess was also performed following the old wound scar, and two tubes were placed again submandibular, which were removed five days after the surgical treatment. In addition, an adjuvant cycle of antibiotics, as previously indicated, was prescribed. The postoperative orthopantomograph showed vital alveolar bone after mandible decortication without signs of osteonecrosis (Figure 7). A hypoesthesia of the lower lip was detected the day after surgery. After removing of the sutures 2 weeks post operation, no intraoral sign of wound dehiscence or new bone exposure was detected (Figure 8). At that time, the hypoesthesia of the lower lip was still present, and the patient was given control appointments every week for clinical evaluation of the surgical side as well as the neural alteration.

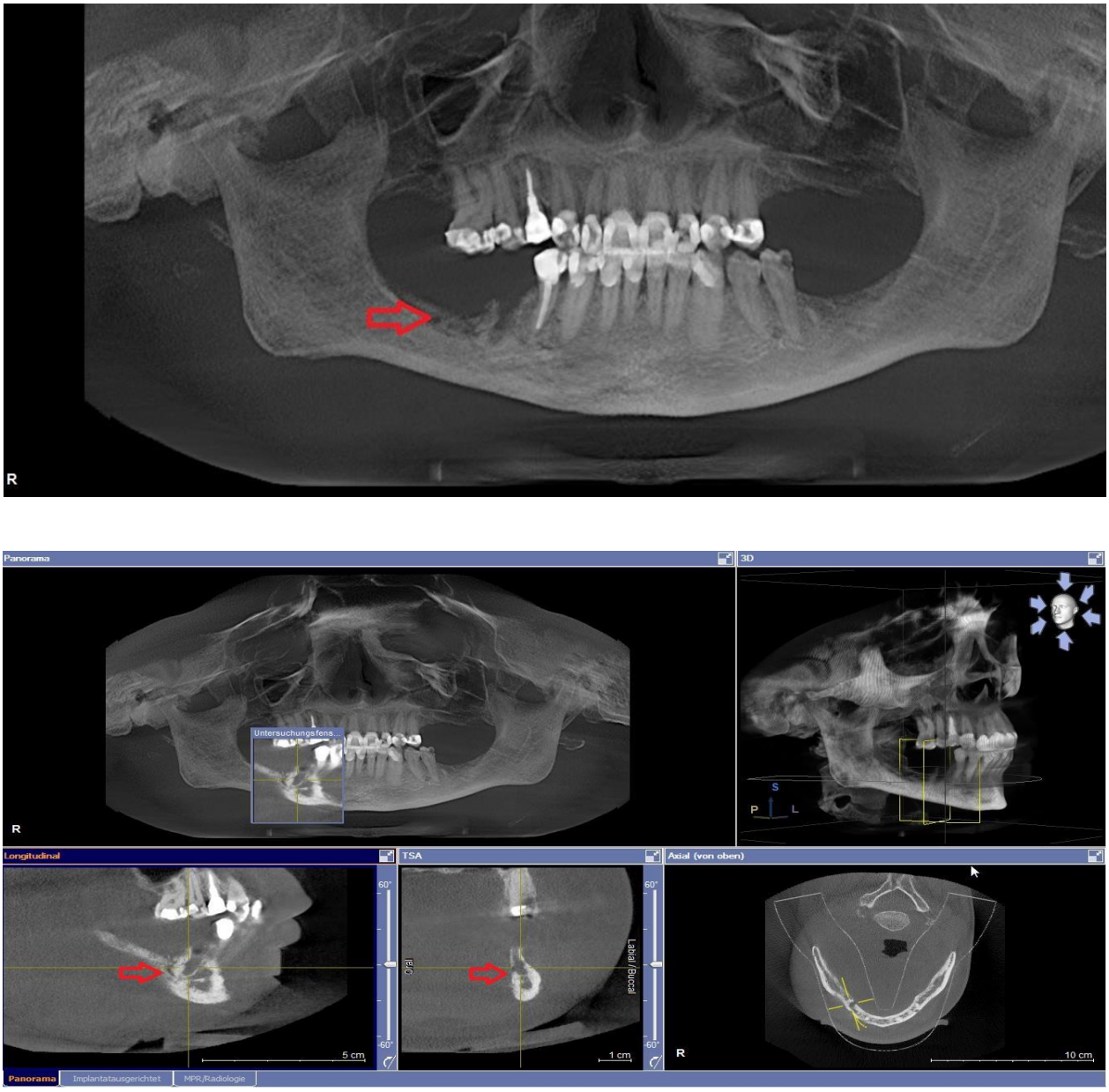


Figure 5: Panoramic view 5 weeks after surgery, showing diffuse bone resorption of the mandible in the region of alveolar exposure (A), radiographic signs that match to the diagnosis of MRONJ. Digital volume tomography showing the loss of bony trabecular architecture and bony lysis with local penetration of the lingual cortical plate (B).

The surgical specimen was fixed in neutral-buffered formalin and sent to the pathological anatomy department of our hospital, where it was decalcified in formic acid, embedded in paraffin, sectioned at 4-μm thickness, and stained with hematoxylin-eosin. The histopathological analysis of the decalcified samples showed areas of bone necrosis with inflammatory cell infiltration and several basophilic bacterial colonies, empty Haversian canals without residual osteocytes/osteoblasts, and reduction of Haversian blood vessels, thus confirming the clinical diagnosis of MRONJ.

Following the surgical treatment, both intra and extra-oral wounds healed without further complications and without recurrence after 3 months of clinical and radiological follow-up. No further prosthetic rehabilitation has been planned for the function and aesthetics of the posterior mandible until January 2020.

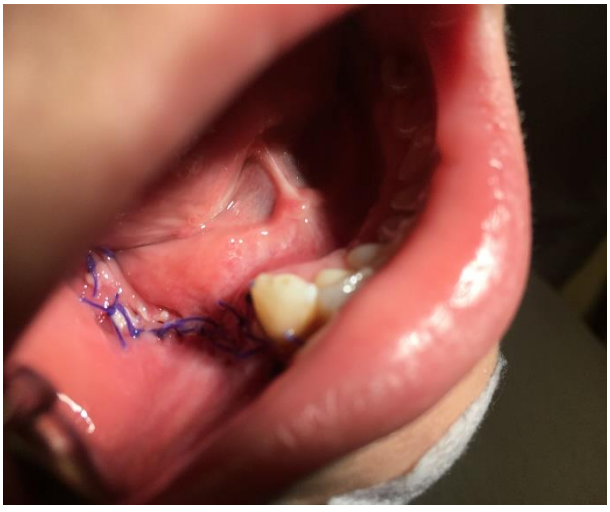


Figure 6: Tension free wound closure after periosteal incisions to avoid recurrence of bone exposure.

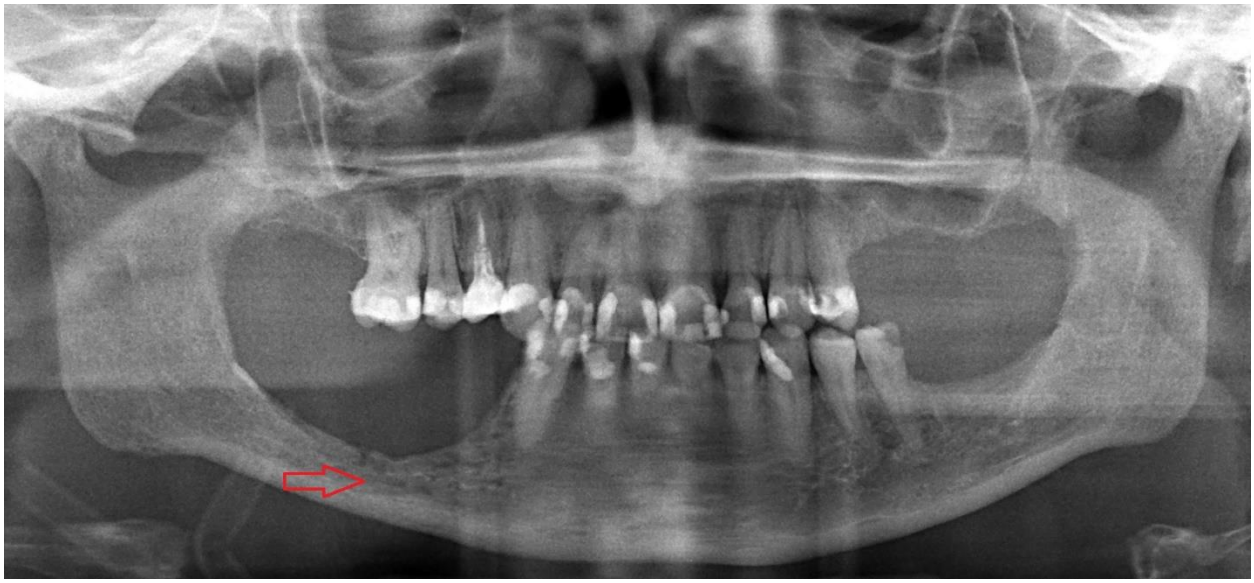


Figure 7: Panoramic radiograph after surgical decortication, presenting the remaining vital alveolar bone.

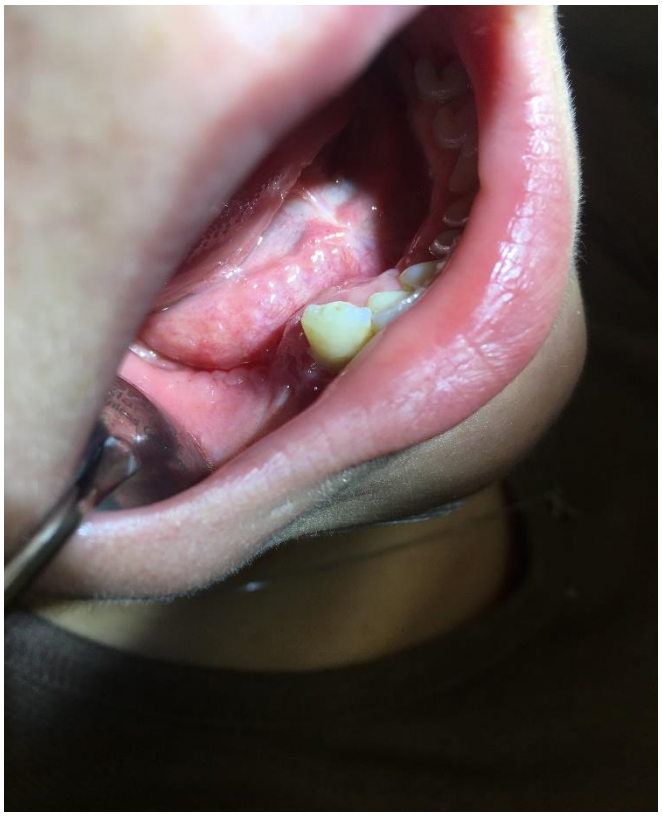


Figure 8: Clinical feature 2 weeks after surgical decortication and sutures removal. No signs of wound dehiscence or bone exposure detected.

DISCUSSION

MRONJ caused by intravenous and oral bisphosphonates has been extensively researched over the last years. Presently, inhibitors of RANKL (denosumab), of angiogenesis (bevacizumab and rituximab), of tyrosine kinase receptors (sunitinib), and of TNF (adalimumab) have already been related to MRONJ in distinct case reports, thus prompting the change in international nomenclature from bisphosphonate-related osteonecrosis of the jaw (BRONJ) to medication-related osteonecrosis of the jaw (MRONJ) [1,19-24].

This paper depicts a clinical case of infliximab-related MRONJ in a patient affected by Crohn's disease, who is receiving 250 mg intravenously every seven weeks for 8 years, combined with oral costicosteroids. A similar case of MRONJ, possibly related to infliximab therapy, was reported by Favia et al. in 2017 in a patient with Crohn's disease. They diagnosed a severe osteonecrosis of the anterior mandible with extraoral necrotic bone exposure and an intra-extra-oral fistula with pus discharge. The alveolar process in the anterior mandible was osteolysed, involving the lingual cortical plate up to the inferior margin. A similar out therapeutic procedure was followed, consisting wide bone resection and debridgment of necrotic tissues [15]. Another incidence of mandibular osteomyelitis was reported by Ebker et al. in a patient with rheumatoid arthritis treated with infliximab [16]. However, the fact that the same patient had been also simultaneously treated with bisphosphonates did not clarify the role of infliximab in the onset of MRONJ. However it did point out the possible potential to the pathomechanism. A report from England in 2007 also presented the development of mandibular osteomyelitis after surgical extraction in a patient diagnosed with idiopathic juvenile arthritis following infliximab administration. The clinicians described mandibular osteomyelitis as a potential complication of infliximab, highlighting its use as risk factor in oral surgery [17]. A case of osteonecrosis of the jaw in a patient with a medical history of Crohn's disease and gastrointestinal remission undergoing adalimumab therapy, another TNF-a inhibitor, was also reported [13]. However, the role of this anti-TNF-α antibody therapy to the manifestation of osteonecrosis in this case was not clearly established due to the concomitant administration of bisphosphonates. Brijs et al. (2019) investigated the occurrence of MRONJ in a population of patients with inflammatory bowel disease treated with TNF-a inhibitors at a tertiary care medical center over a 24-year period [18]. These patients were cross-matched with all patients diagnosed with MRONJ. This resulted in three patients with a definite diagnosis of MRONJ, without concomitant treatment with bisphosphonates. This study identified and described anti-TNF-α-related MRONJ occurring in a large cohort of patients with inflammatory bowel disease [18]. In the current case, mandibular osteonecrosis developed after

years of infliximab treatment, without bisphosphonate administration, but in co-therapy with corticosteroids. After surgical removal of the second premolar which caused the perimandibular abscess no complete bone healing was recorded, leading to the diagnosis of MRONJ. The bony lesion was defined as stage 3 according to the AAOMS staging system, due to its severity, with intraoral bone exposure and with osteolysis extending to the inferior border of the mandible [1]. Following intravenous antibiotic cycles during hospital administration, the patient underwent surgical therapy with the debridement of the lysed alveolar bone and extraoral abscess incision. The histopathological analysis of the surgical specimen confirmed the diagnosis of MRONJ.

TNF-α plays an important role in systemic bone loss and turnover, promoting osteoclasts and osteoblasts activity. Due to its central role in the body's defense against infection, it is responsible for formation of granulomas and intracellular killing of pathogens that have been engulfed by macrophages [15,26]. Anti-TNF-α biologics are possibly responsible for bone turnover inhibition, probably by reduction of RANKL, thus resulting in an osteoclast function inhibition [8,15]. Anti-TNF-α antibodies inhibit the induction of interleukins, enhancement of leukocyte migration and expression of adhesion molecules. Such anti-TNF-α-mediated reduction of systemic bone loss may certainly increase the risk of MRONJ [15,20], similarly to what was detected in patients taking bisphosphonates or denosumab, the latter also acting as inhibitors of osteoclast functions [15,26-27]. Infliximab is a genetically engineered chimeric human/mouse monoclonal antibody, which highly agrees to and binds to both the soluble and the transmembrane forms of human TNF-α, a key mediator of mucosal inflammation [15,25]. Infliximab as a TNF-a inhibitor has been increasingly been used to treat autoimmune inflammatory conditions such as active Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and rheumatoid arthritis [15,17]. In his review in 2004, Scheinfeld reported the most important side effects related to infliximab, including lymphoma, infectious diseases, congestive heart failure, demyelinating disease, lupus-like syndromes, induction of autoantibodies, reactions at the injection site, and diabetes mellitus [11]. To date, the potential role of infliximab treatment for the pathomechanism of MRONJ has been sparsely elucidated in publications [15-18]. However, we notice that therapy with TNF-a inhibitors, such infliximab, may facilitate infectious healing complications to patients undergoing oral surgery due to the immunosuppression caused.

We recognize several limitations to this case report. No safe conclusion with regards to the occurrence of MRONJ related to infliximab and other TNF-a inhibitors can be made without further prospective studies with a satisfied patient's collective and standardized evaluation protocol. The patients and the medication factors, such as the duration of the treatment with infliximab, concomitant therapies with corticosteroids or other biological agents, diabetes mellitus or other autoimmune diseases, presence of marginal or apical periodontitis before medication beginning and mouth hygiene of the patient should be also investigated in order to isolate the role of infliximab to the pathogenesis of MRONJ. Furthermore, it remains unknown to what extent TNF- a inhibitors can cause MRONJ after discontinuation of the biological agent [18]. For example, the effect of denosumab on bone metabolism dissipates after 6 months, because it is not retained in the bone, unlike bisphosphonates [1,18]. Like denosumab, TNF-a inhibitors are monoclonal antibodies and their effect on bone metabolism is probably also explained by temporal interactions with their receptor [18]. Consequently, it would seem that an association between TNF-a inhibitors and MRONJ can only be assumed when the patient is on current treatment with a TNF-a inhibitor or has been on treatment in the past few months. In summary, considering the nature of case reports like ours and the current lack of prospective studies, we can only assume causality between TNF-a inhibitors such as infliximab and MRONJ.

CONCLUSION

We reported a case of severe jaw osteonecrosis in a patient following infliximab therapy. Future studies with prospective design considering other confounding factors should continue to register the occurrence of MRONJ in patients treated with infliximab and other biologicals, in order to confirm the role and research the causality. However, a regular dental check-up before and during infliximab therapy is strongly recommended in order to prevent MRONJ recurring or to detect lesions at earlier stages.

Furthermore, considering the increasing number of medications related to the MRONJ onset, the prescription of all biologicals should require more attentive evaluation of well-known risk factors for MRONJ by all the prescribing specialists. The role of gastroenterologists and rheumatologists is especially important due to the large number of autoimmune diseases, which require the administration of new biological drugs, thus these patients are potentially at risk of MRONJ.

Ethical Statement

This research was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki. The patients' data was referenced to with the understanding and written consent of the patient, and all data was also anonymized and de-identified prior to analysis. Reporting was based on the recommendations of the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" initiative [28].

Competing Interests

The authors declare that they have no competing or financial interests, either directly or indirectly, in the products listed in the study.

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