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Case Report

Denosumab-related osteonecrosis of the jaw in a patient with osteoporosis: case report

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Abstract:

We report a case of osteonecrosis of the jaw (ONJ) associated with denosumab therapy in a 69-year-old female patient being treated for osteoporosis. The patient was admitted in Oral and maxillofacial surgery clinic twice because of nonhealing extraction wounds and inflammatory complications. We recommend conservative therapeutic approach and avoidance of extensive surgery in patients with ONJ.

I. **Introduction:**

Bisphosphonates (BPs), monoclonal antibodies and anti-angiogenic drugs are widely used to treat diseases affecting the bone remodeling such as osteoporosis, bone metastasis and multiple myeloma [0,[2]]. These medications are able to inhibit osteoclasts' function (osteoclast-induced resorption) and reduce bone turnover. Since their introduction many cases of patients with medication related osteonecrosis of the jaws (MRONJ) have been reported in the literature. Usually osteonecrosis of the jaw (ONJ) is found after invasive dental treatment or trauma (i.e. ill-fitting dentures). However, spontaneous cases of MRONJ have also been presented [[3]]. The etiology of MRONJ is considered to be due to hypovascular and hypocellular bone, local tissue hypoxia and mucosal dehiscence.

In recent years, investigators have described the incidence of bone necrosis in cancer patients treated with antiresorptive agents like denosumab (Prolia, Xgeva) [[4]]. Denosumab interfere with osteoclastogenesis via inhibition of differentiation and survival of osteoclasts [[4]]. Our aim is to describe a case of a patient, having multiple systemic diseases, admitted in our hospital with denosumab induced jaw necrosis. We would like to alert dentists and oncologists to the high chance that the number of ONJ cases will significantly increase, as these medications became more commonly prescribed and the prevention of complications is of highly importance.

II. Case Report:

We present a clinical case report of 69-years old female patient who sought care at the maxillofacial surgery clinic twice within the past 6 months. The patient was firstly admitted in the clinic in May 2018 with 2-weeks history of swelling around the body of the mandible on the left side, suppuration and pain in region of already extracted teeth – mandibular left second and third molars. The teeth have been extracted in June 2017. Since then the patient is having multiple episodes of severe pain and edema. Various antibiotics for oral administration (ciprofloxacin, augmentin, etc.) have been prescribed with just temporary therapeutic effect. The patient is having history of osteoporosis and has completed a short course of Fosamax in 2014 followed by denosumab therapy from 2014 till 2017. She also suffers of rheumatoid arthritis, Sjogren syndrome, Raynaud syndrome, microvascular coronary disease, ischemic heart disease, Hashimoto disease, medication-induced hypercorticism. The patient is slow-moving and asthenic because of the generally impaired health status.

Extraorally, the skin on the face in found extremely dry, red and teleangiectatic. Multiple ecchymosis are observed on the extremities. On the intraoral clinical examination the patient is having an ulcerated area with nearly 2cm exposed necrotic bone in the region of the extracted teeth (mandibular left second and third molars) with pus discharge and soft tissue edema. Restrictions in the lower jaw movements were observed due to the inflammation. Enlarged submandibular lymph nodes on the ipsilateral side were found on palpation. Nonhomogeneous radiolucency without clear borders and with no well-defined demarcation of sequestrum in the left mandible is seen on the panoramic X-ray. CT-scan data confirmed necrosis there. We therefore established a diagnosis of denosumab-related ONJ. The therapeutic approach included intravenously given antibiotics (ceftriaxone, metrodinazole) and local surgical debridement, without flap, of the necrotic bone in the affected area. No extensive surgical procedures were conducted. Follow-up examinations within the next

couple of months reveal no local complications and no evidence of recurrence.

In October 2018 the same patient was admitted in the clinic for the second time. The current complaints were pain and edema in the region of the mentum and in the mandibular frontal teeth, pain in the right mandible irradiating towards the right ear. The patient was having pain on swallowing without any symptoms of trismus. Extraorally, significantly firm swelling and erythema in the submental region are observed with enlarged and painful regional lymph nodes. First to second stage tooth mobility is found in the region of the mandibular frontal teeth on the clinical examination with mild symptoms of gingival inflammation. Painful inflammatory infiltrate is found on palpation in the right sublingual space. Both the tongue and the sublingual glands and elevated due to the swelling. Scarce fluid outflows of the submandibular and sublingual duct openings. No exposed necrotic bone is seen in the oral cavity. No significant radiographic changes are observed and there is no clear evidence of bone necrosis in the region of the abscess. Inraoral incision and drainage are the treatment of choice. Nearly 6mL purulent exudate was evacuated. No additional surgery was performed.

The reported clinical case presents a patient with multiple systemic diseases and progressive MRONJ. Conservative therapy and long term follow-up is our treatment of choice.

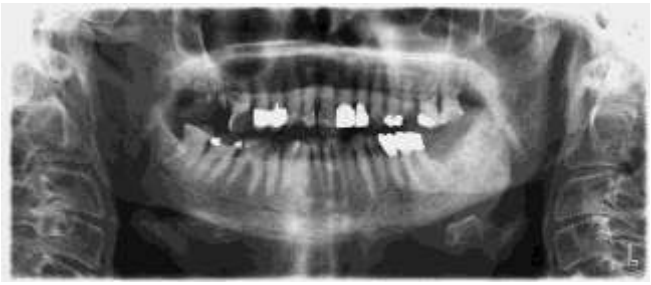

Figure 1 Panoramic X-ray of a patient with denosumab-induced ONJ

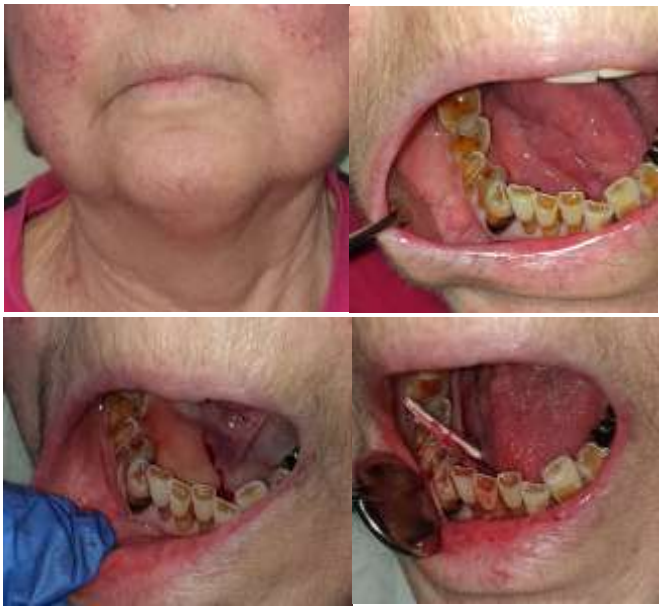

Figure 2 Extra- and intraoral status of a patient with denosumab-related ONJ

III. Discussion:

Denosumab is a monoclonal antibody with high affinity to Receptor activator of nuclear factor-kappa B (RANK) ligand. It is classified as antiresoptive agent with ability to block the interaction between RANK ligands and RANK receptors, thus preventing bone resorption via the inhibition of osteoclasts differentiation and activation [[5]]. Denosumab increases bone mineral density in women with postmenopausal osteoporosis and in men on androgen-deprivation therapy for nonmetastatic prostate cancer [[6]].

As antiresoptive, drug denosumab has different mechanism of action than BFs. Its activity is strongly directed to the osteoclast precursors formation via inhibition of RANK ligands action. It well documented that denosumab is having some benefits over BFs [[7]]. Denosumab provides greater effectiveness and lower risk of adverse acute and chronic side reactions, i.e. arthralgia, pyrexia, renal failure, etc. However, evidence show that monoclonal antibodies application is also associated with high risk of MRONJ [[8],[9]]. It is reported that the combined application of BFs and anti-angiogenic drugs is patients with renal carcinoma and bone involvement improves the treatment efficacy but increases the risk of bone necrosis [[10]]. Furthermore, the duration of BF and/or antiresorptive therapy is considered risk factor for ONJ. Henry et al. [[11]] concluded that in cancer patients treated with zoledronic acid or denosumab the incidence of ONJ is, respectively, 0,6% or 0,5% at 1 year; 0,9% or 1,1% at 2 years; 1,3% or 1,1% at 3 years.

To the best of our knowledge, the first clinical case of a patient with denosumab-induced ONJ was reported in 2010 by Taylor et al. [[12]]. In their case the patient with cancer is receiving denosumab and did not have any history of bisphosphonates or radiation therapy. Since the introduction of monoclonal antibodies in the clinical practice the number of patients with ONJ is increasing constantly. Currently is debated whether the surgical or the conservative treatment is followed by better therapeutic outcome. Diz et al. [[6]] hypothesized that in patients receiving denosumab , a sufficient preventive dental care and non-invasive dental treatment during the denosumab intake may reduce the risk of ONJ development and progression. Other authors also stated that more conservative treatment of denosumab related ONJ is associated with lower risk of additional complications [13],[14].

We present a clinical case of a patient with denosumab-related ONJ after extraction of 2 teeth. The chief complaints of pain and edema recurrence, together with non-healing extraction wounds are observed within the past 1 year. In our case extensive surgical treatment is undoubtedly avoided. We also recommend more conservative treatment approach and long term follow-up in patients taking monoclonal antibodies. Thus we aim to decrease the risk of more diffuse necrotic bone exposure and additional more serious complications (i.e. bone sequestration, pathological fractures, fistula formation, etc.).

IV. Conclusion:

Based on our findings, it is concluded that highest number of

cases with RANK ligands-associated ONJ was related to treatment of osteoporosis, bone metastasis and multiple myeloma. Dentists should be aware and better informed about the most appropriate treatment approaches and prevention of ONJ in patients receiving monoclonal antibodies. Local factors seem to be important for triggering the adverse effects of the monoclonal antibodies treatment. Although, there is no consensus about the therapy, the prevention, mouthwashes, antibiotic treatment with conservative surgical debridement and avoidance of extensive surgical procedures are shown to be effective in most cases.

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