

Case Report,

Treatment of Medication-Related Osteonecrosis of the Jaw of a Patient with Immediate Implants

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Abstract:

The aim of this paper is to present the case of a 73 year old man with immediate implants who was admitted to the Clinic of Maxillofacial Surgery for treatment of medication-related osteonecrosis of the upper right jaw. The problem occurred after the extraction of two teeth, without considering that the patient is undergoing chemotherapy with Xgeva. The patient was diagnosed with prostate cancer in 2013. In 2015 were found metastases on the bones. According to the particular characteristics of the patient he underwent surgery under general anesthesia. The innovation in our case is that we used a placement of a PRF membrane and plastic closure of the wound. This is a new and alternative treatment method and there were no postoperative complications or wound infections, which are usually common in the postoperative period for people with medication-related osteonecrosis of the jaws.

Introduction: The Medication-related osteonecrosis of the jaws (MRONJ) is a common side effect of drug therapy applied to cancer patients for bone metastasis, multiple myeloma, and osteoporosis. It is described as a presence of open necrotic bone in the maxillofacial area that does not heal for more than 8 weeks and affects patients who have cancer and have undergone long-term intravenous bisphosphonates, denosumab and anti-angiogenic drugs, but without a history of jaw radiation therapy. Most cases of MRONJ occur after surgical procedures on the oral tissues. MRONJ has a negative effect on quality of life, and can result in reduced social contact, pain and masticatory difficulties. The treatment of MRONJ can be conservative or surgical, and there is no consensus on which method is more effective in terms of treatment outcomes. It depends on the severity and classification of MRONJ. Surgical treatment remains one of the most reliable methods, but it must also undergo its modernization and take advantage of progress in research and development of new technologies that provide the opportunity for relatively easy and affordable use of new growth factors in maxillofacial surgery.

Case report: The main purpose of the article is to present a case of patient, diagnosed with the condition medication-related osteonecrosis of the jaw, who underwent surgical treatment in Clinic of Maxillo-facial Surgery. The subtlety of the surgery was the use of platelet-rich fibrin membrane (PRFm) which is easy to prepare and apply and shows promising results in wound healing and periodontal regeneration.

Conclusion: The article aims to provoke awareness of few things. On one side the positive result of using new alternative method of surgical treatment of MRONJ – the platelet-rich fibrin membrane. The second important thing is that the case highlights the importance of improvement of oral hygiene and the need of regular dental examinations in cancer patients after drug therapy, because this will minimize the development of MRONJ. Third, but not least – dentists should be very careful with their cancer patients and to refer them to oral and maxillofacial surgeons, experienced in the treatment of patients with MRONJ.

Keywords: osteonecrosis, medication-related osteonecrosis of the jaw, bisphosphonates, denosumab, platelet-rich fibrin membrane, immediate implants, prevention.

Introduction:

The American association of oral and maxillofacial surgeons (AAOMS) defines the Medication-related osteonecrosis of the jaws as the presence of open necrotic bone in the maxillofacial area that does not heal for more than 8 weeks and affects patients who have cancer and have undergone long-term intravenous treatment with bisphosphonates, denosumab and/or anti-angiogenic drugs, but without a history of jaw radiation therapy.¹⁻⁶ Open necrotic bone in the oral cavity is only one of the possible manifestations of the disease and it does not occur in all patients. Most cases of MRONJ occur after surgical procedures on the oral tissues.⁷ However, 30% of cases occur spontaneously.⁸

The incidence of MRONJ is twice as high in the mandible (77%) as in the maxilla and higher in women (72%) than in men.⁹ The risk of MRONJ in cancer patients on bisphosphonates therapy is approximately 1% (100 cases per 10,000 patients) and almost the same is the risk for patients on RANKL inhibiting treatment with denosumab.¹⁰ In addition to the medication-related, there are also other risk factors, such as local ones – tooth extraction or other dentoalveolar procedures, as well as demographic and systemic ones – age, sex, corticosteroids, tobacco use, etc.¹¹ MRONJ has a negative effect on quality of life, and can result in reduced social contact, pain and masticatory difficulties.¹⁰

In 2003 Marx reported the first cases of unusual oral lesions in the jaws of patients suffering from multiple myeloma and metastatic bone disease.^{5,12,13} It is interesting to mention that similar cases of osteonecrosis of the jaw have been described as early as the 19th and early 20th centuries in patients exposed to white phosphorus, a condition called "fixed jaw" or "phosphorus necrosis".¹⁴

There are four stages of MRONJ and AAOMS offers different strategies for diagnosis and treatment for each of them.¹⁵ But the dynamic nature of the staging system is a matter of debate. For example, stage 1 MRONJ may become stage 2 after infection, and stage 2 disease may be reduced to stage 1 after a short course of antibiotics.¹⁵

The treatment of MRONJ can be conservative or surgical, and there is no consensus on which method is more effective in terms of treatment outcomes.¹⁶ It depends on the severity and classification of MRONJ. Conservative treatment

includes pain control, antibiotics and antibacterial rinses.¹⁰ The use of antimicrobial mouthwashes in combination with an oral antibiotic (penicillin, metronidazole, clindamycin, doxycycline, erythromycin etc.) gives results only in the initial stage of treatment and can be used rather to stop the development of disease than for its treatment.¹⁷⁻

¹⁹ Surgical treatment remains one of the most reliable methods, but it must also undergo its modernization and take advantage of progress in research and development of new technologies that provide the opportunity for relatively easy and affordable use of new growth factors in maxillofacial surgery.^{2,20} As a result of advances in research and the development of technology today, classical surgical techniques are combined with biological approaches such as the use of growth factors.^{2,20} One of these achievements is the platelet-rich fibrin membrane (PRFm), which can be obtained in an easy and affordable way in an outpatient setting and is a new alternative method for the treatment of MRONJ. Platelet-rich fibrin membranes are used to stimulate the healing process in the bones and soft tissues and reduce the wound healing time².

Case report:

The patient in our case report is a 73 year old man who is admitted for treatment of medication-related osteonecrosis of the upper right jaw. The patient has immediate implants after tooth extraction, without considering that he is undergoing chemotherapy due to metastasis of bones.

Detailed medical history revealed that the patient was diagnosed with prostate cancer in 2013. In 2015 were found bone metastases. Since then the patient was treated with intravenous administration with Xgeva. In 2020 two of his teeth were extracted and immediately after that two dental implants were surgically placed. Two months after the surgery severe pain and inflammation appear around one of the implants. Soon there was strong mobility around the implant and it fell out. The wound did not heal for a long time. Treatment with ionophoresis and an unsuccessful attempt for plastic closure of the wound were performed. Then the patient was diagnosed with medication-related osteonecrosis on the jaw (Fig.1).



Figure1: MRONJ before surgery

According to the particular characteristics of the patient and adapting the best treatment for his needs he underwent surgery under general anesthesia. The surgical treatment included excision and removal of the sequestration in the area of the osteonecrotic focus (Fig.2), placement of a PRF membrane (Fig.3-4) and plastic closure of the wound (Fig.5).



Figure2: Sequestra



Figure3: PRF membrane

The surgical wound healed successfully and the patient responded well to the procedure. There were no postoperative complications or wound infections, which are usually common in the postoperative period for people with MRONJ.



Figure4: Placement of a PRF membrane



Figure5: Suturing the wound

Discussion:

Aminobisphosphonates, antiresorptive or antiangiogenic drugs are often prescribed to treat patients with breast or prostate cancer, bone metastases from solid tumors, malignant hypercalcemia, multiple myeloma or osteoporosis.⁶ In the case of our patient; he was undergoing chemotherapy with denosumab (Xgeva). This drug has been shown to be superior to zoledronic acid in delaying or preventing skeletal-related events in patients with bone metastatic breast cancer.^{21,22}

Unlike bisphosphonates, denosumab does not accumulate in the bones and has a half-life of 26 days, with its effects dissipated within 6 months of stopping treatment. On the other hand, the half-life of bisphosphonates is 10 to 12 years and they persist in the bones for years after their cessation.²³

This is why many practitioners consider denosumab to be a less aggressive drug, which is a more conservative therapeutic approach. At the same time, denosumab was associated with a higher incidence of MRONJ.^{6,24,25}

Based on clinical and epidemiological findings there is a high risk dental extraction to result in MRONJ especially in case of patients who were medically treated with bisphosphonates and RANKL inhibitors as it is in the case of this patient – with Xgeva.² Therefore tooth extractions and dental surgical procedures like implants, especially immediate ones, are also considered as risk factors for the development of MRONJ and some guidelines even recommend avoiding tooth extractions and dental surgery when taking bisphosphonates whenever possible.^{20,26}

There are various protocols for the treatment of MRONJ which are recommended in the literature, ranging from local deblocking of the necrotic lesion to more invasive radical resection of the diseased jawbone, but there are still no clear treatment guidelines for the disease with predictable clinical outcome.^{2,27,28} Therefore, the decision to take a conservative approach or to undergo more invasive surgery is mainly based on expert opinion. In our case, we decided to apply a new alternative method of treating MRONJ by using platelet-rich fibrin membrane (PRFm).

Dohan et al. (2006) developed a production protocol for PRF in an attempt to platelet aggregate and release cytokines in a fibrin clot. Platelets and leukocytes are an important part of this biomaterial, and the fibrin matrix that supports them is very useful in compiling the responsible determinants of the therapeutic potential of PRF.²⁹

The results of studies related to the biological effects of PRF lead to its increasing use in dentistry. Among the advantages of PRF we can mention the easy preparation/application; lack of biochemical modification; simplified and cost-effective process; long-term effect; maintains and accelerates the healing process due to the slow polymerization; helps with hemostasis; the three-dimensional structure gives elasticity and flexibility to the PRF membrane.^{2,17}

The use of a PRF membrane as an adjunct to wound healing and periodontal regeneration shows promising results^{2,30}. In addition to the procoagulant effects of platelets, PRF is a source of growth factors involved in wound healing by clot formation.³¹ It is successfully used for correction of bone defects in periodontology, oral and maxillofacial surgery and implant dentistry.

The increasing incidence of MRONJ is a fact that needs to be addressed in the medical community and in particular among general dentists, who often meet with such patients while routine dental care.³²

Understanding the side effects of RANKL inhibitors and the potential rapid progression of osteonecrosis, especially in cases where patients have switched from denosumab bisphosphonates, can raise awareness and collaboration between oncologists and dentists and provide appropriate prevention and treatment options for these patients.⁶

Educating patients about the signs and symptoms of MRONJ is also very important. All patients should be informed of the risks and advised to contact their periodontist or oral surgeon immediately if they notice any pain or swelling in the jaws, loose teeth, pus, bad taste or tingling, or any unusual sensation in the mouth². Patients at risk also should have a thorough periodontal and dental examination before initiating antiresorptive therapy.⁶ Invasive dental procedures should be avoided in high-risk patients unless there are dental infections that cannot be controlled with standard therapies.² Before starting invasive dental procedures, such as tooth extraction or, as in our case, immediate implant placement, the dentist has the responsibility to assess the medical history and reassess the risk of MRONJ. The medical history should determine what dose of bisphosphonate or denosumab the patient is receiving, the duration of this treatment, and whether other drugs are used that may increase the risk of MRONJ². If they suspect the risk of MRONJ, dentists should contact their physician and refer the patient to an oral and

maxillofacial surgeon or oral cancer center experienced in the treatment of patients with MRONJ.²

Focusing on careful oral hygiene and the absence of dental trauma will reduce the chance of developing MRONJ or at least allow early detection of smaller necrotic lesions and successful non-surgical treatment.^{10,11} Prevention of MRONJ or overall management of these patients is not possible without good cooperation between oncologists and dentists.⁶

Conclusion:

The incidence of MRONJ worldwide is increasing along with the increase in prescribed bisphosphonates³⁰. The most effective approach in cancer patients is the prevention of MRONJ. Effective prevention or early identification of MRONJ in patients treated with denosumab or bisphosphonates depends on the awareness of patients and practitioners of the associated adverse events.⁶ In this sense, dentists play a key role in minimizing the risk of developing MRONJ in patients.¹⁰ Studies show that the risk of developing the condition can be significantly reduced if patients are assessed by a dentist and preventive measures are taken.¹¹

Dentists should be familiar with the clinical presentation of the disease. Because bisphosphonates and denosumab play an important role in the management of cancer and metastatic bone disease, they will be used in the future until a possible replacement with fewer side effects is launched. Therefore, dentists should focus on the proper management of dental and periodontal diseases before starting treatment with bisphosphonates and denosumab to prevent BRONJ and to routinely monitor such patients during their treatment.³²

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