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Medication-Related Osteonecrosis of the Jaw (MRONJ) as a Consequence of Multiple Sclerosis Treatment

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Aim

To report a possible case of Mronj in a MS patient due to ocrelizumab

Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a serious pathological condition that is usually caused by anti-resorptive or anti-angiogenic drugs, but at the same time, MRONJ may be induced by drugs which have no effect on bones or blood vessels. Here we report an atypical case of MRONJ in a female patient due to the administration of Ocrelizumab as a treatment for multiple sclerosis (MS).

Case Report: A 49-year-old female was referred to Shahab Oral Medicine and Special Care Dentistry Clinic in Aug 2022 with the chief complaint of severe gum pain. In clinical examination, it was found that the socket of extracted tooth, the second molar of the left side of the mandible, was still recovering after five months and accompanied by severe pain in touch and exudative secretions and incomplete recovery of Mucosa with a depression on the level it. At the same time the pain was relieved after using antibiotics, but as soon as she stopped the antibiotics, not only the pain started again in the area, but also it got worsen. In patient's medical history, it was revealed that she had been

suffering of MS since 2007, and in addition to the long history of using Ibuprofen, Baclofen, Sertraline and Fampridine, had received the first injection dose of Ocrelizumab six months ago. According to the clinical and radiographical evidences of a none-healing socket and medical and dental history of the patient, the lesion was diagnosed as MRONJ, so that antibiotics, painkillers and chlorhexidine mouthwash were prescribed for her. Two weeks later, on her first follow-up, the patient's pain decreased and other symptoms had stopped. As a result, it seems that according to the fact that no other known factor was found to cause MRONJ in this patient and previous studies confirms the relationship between Rituximab and MRONJ, there also might be a relationship between Ocrelizumab and MRONJ.

Conclusion: It should be noted that to confirm MRONJ as a complication of Ocrelizumab, more clinical studies a with larger number of patients using this drug are recommended.

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon and potentially serious adverse side effect of anti resorptive and anti angiogenic drugs. It can cause chronic pain, infection, dysfunction, and disfigurement and also can affect the quality of life of individuals. MRONJ is also defined as an oral complication in the form of exposed bone or a bone which would be probed through an intraoral or extraoral fistula in the orofacial region which have been remained in patient's mouth for more than eight weeks, but at the same time, the patient shouldn't have a history of radiation therapy or metastatic disease in jaws. [1-3]

Anti resorptive drugs, including nitrogen-containing bisphosphonates (N-BPs), such as Zoledronic acid, Alendronate, and Anti-Rankl antibodies (receptor activator of nuclear factor kappa-B ligand) like Denosumab, are used to manage bone metastasis in patients with cancer (breast, prostate, multiple myeloma) or to prevent fractures in patients with osteoporosis. Although significant advances have been made in the diagnosis of MRONJ, its pathophysiology has not been fully elucidated yet.In general, the diagnosis of MRONJ is based on radiographic evidences, clinical symptoms and the patient's medical history, and the final diagnosis is based on the combination of these factors. [4, 5]

Multiple sclerosis (MS) is an autoimmune neurodegenerative inflammatory disease in central nervous system (CNS), which is characterized by inflammatory demyelination of nerves and axonal/neuronal damage. [6] The use of monoclonal antibodies that destroy B cells as a treatment for autoimmune diseases including MS, has increased in recent years because the fact that B cells play a major role in the pathogenesis of MS.Since Rituximab, the first chimeric B-cell-destroying monoclonal antibody, showed efficacy in MS clinical trials, researchers evaluated the effectiveness of a human anti-CD20 antibody called Ocrelizumab . This immunosuppressive drug is our target in this study and reduces the intensity of relapsing-remitting MS activity in primary progressive MS. [7]

According to the available articles, there have been cases of MRONJ due to other immunosuppressive drugs such as romosozumab, adalimumab, infliximab and Rituximab, which are used to treat other kinds of autoimmune diseases, but occurrence of MRONJ due to Ocrelizumab has not been reported so far. [8-10]

Case Report

A 49-year-old female patient was referred to Shahab Oral Medicine and Special Care Dentistry Clinic on August 2022, with a chief complaint of severe and debilitating gum pain (to the extent that she wasn't able to eat) on the left side of the mandible since 6 months ago. In early clinical examination, it was observed that the socket of the extracted molar hadn't been healed and there was a depression on the level of unhealed mucosa with exudative secretions under pressure and severe pain in touching. We also noted that the area was free of active purulent secretions. (Figure 1)

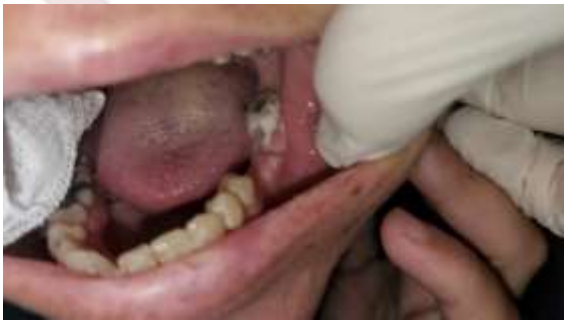

Figure 1: Clinical image of an extraction site with incomplete mucosal healing, second molar of left mandible region

In patient's dental history, it was determined that despite the fact that there was no sign of decay or loosening or any other reason for extraction of the 2nd molar, it was extracted just because of the severe pain. The pain decreased only during the short time of taking antibiotics prescribed by the dentist after extraction. As she stopped the antibiotics, the pain got worse. Unfortunately, the pre-extraction radiographic cliché was not available. In the panoramic image, we found signs of an incomplete healed socket of the extracted tooth with a sclerosing area around it. (Figure2) In her medical history, in addition to MS, some cognitive and neurological disorders such as depression and anxiety were mentioned, but no history of other autoimmune disease like Arthritis Rheumatoid or radiation therapy, cancer, osteoporosis. she also hadn't been abusing drugs. we also noted that no one in her family had a history of MS.

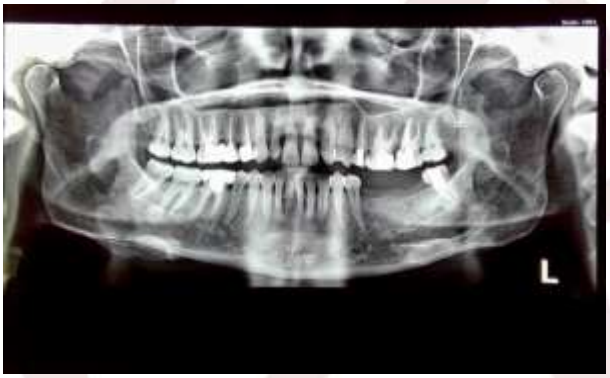

Figure 2: Panoramic view of an incomplete healed socket of the extracted tooth with a sclerosing area around it after five months

In patient's medical history, it was determined that she had been treated with high dose interferon since 15 years ago until 8 years ago as the first drug prescribed for MS, and had a long history of using ibuprofen, baclofen, sertraline, and fampridine, but no history of corticosteroids or other immunosuppressive and anti-resorptive drugs were reported by the patient. Due to the progressive course of MS symptoms in this patient(EDSS: 6) and increasing MS plaques in the neck area, she was given Ocrelizumab 6 months ago, and 3 weeks after receiving the first dose of it , according to the severe and unbearable pain of second molar of the left mandible, the tooth was extracted .The first differential diagnosis was MRONJ (due to the incomplete healing of the socket area) and the second one was neuralgic pain related to the main disease, which was ruled out after consultation with her neurologist, according to the clinical examinations and the differences in the nature, type, and severity of the pain.

Since CBCT is the gold standard for Diagnosis and differentiating MRONJ from early stages of other types of bone necrosis, CBCT was requested for the patient as a result to the suspicion of MRONJ in this patient and to confirm the diagnosis.[4, 5]Radiographic findings in the CBCT sections from the posterior side of the left mandible were the sclerotic area without any periosteal reaction or sequestration along with the diffuse pattern of trabeculae, lack of complete healing of the tooth socket and evidences of ossification in it (Figure 3).

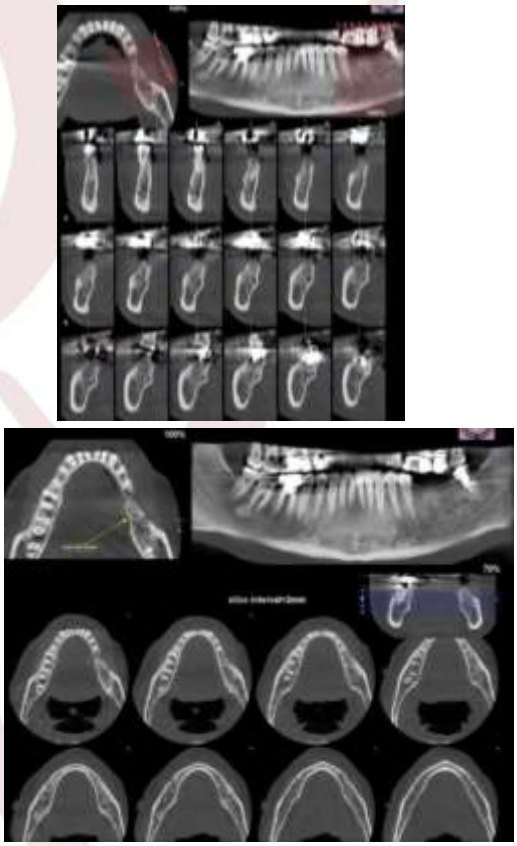

Figure 3: View of incomplete socket healing with highly diffused trabeculae and sclerotic tissue in CBCT images.

Based on the radiological interpretation and the positive clinical symptoms and also according to the patient's medical history and administration of Ocrelizumab, the early stages of MRONJ was suggested as the final diagnosis and patient was advised to avoid any dental treatment and to wash her mouth regularly with sodium chloride mouthwash. Due to the absence of exposed bone in her mouth, the patient was prescribed broad spectrum antibiotics, painkillers and chlorhexidine mouthwash.

Two weeks later, on her first follow-up, the pain and sensitivity in touching and the exudative secretions had been stopped. Just like the initial examination, the area didn't have any sign of active pus secretion. We also consulted with her neurologist to change the drug and choose an alternative one if possible, and the patient's next follow-up was determined for the 6 months later.

Discussion

MRONJ is an adverse, rare and serious oral side effect specific to the Jaw region in a person with a history of treatment with anti-resorptive drugs (for example, Bisphosphonates and Denosumab) or antiangiogenic drugs (for example Bevacizumab). According to recent reports, other drugs, such as tumor necrosis factor (TNF-α) and anti-CD20 antibodies, including rituximab, and some monoclonal antibodies, may probably cause MRONJ. [8-11] The clinical symptoms of MRONJ as a complication of anti-resorptive, anti-angiogenesis drugs and some other drugs with the same side effect are: Pain is the dominant symptom along with exposed bone, inflammation, swelling, bone infection, fistula, purulent secretions, trismus, dysfunction and deformity of the jaw, impaired wound healing and deficiency in immune response to infection, tooth loss and reducing the patient's quality of life. [12, 13]

The diagnosis of MRONJ is based on medical and drug history and clinical and radiographical symptoms of the patient. Its differential diagnosis are osteomyelitis with other causes, bone metastases, and in our case, trigeminal neuralgia. [12]

Our first diagnosis in this case is MRONJ, a chronic sclerosing osteomyelitis which may be induced by the consumption Of Ocrelizumab according to the onset of symptoms which were, three weeks after the first injection and, no history of other immunosuppressive drugs like corticosteroids. Other possible symptoms confirming our possible diagnosis are: lack of other known risk factors of MRONJ and presence of clinical evidences such as; severe pain, the exudative secretions, positive response to the antibiotic treatment and finally radiographic evidences.

Radiographic findings are one of the most important factors for diagnosing MRONJ. In this patient, the appearance of irregular sclerotic tissue with a highly diffuse pattern of trabeculae inside the unhealed socket and bone sclerosis around it with no sign of sequestration or periosteal reactions could indicate to a possible diagnosis of MRONJ. Radiographic findings of MRONJ include bone Excessive density, thickening of the periosteum, bone loss, trabecular changes, osteolysis and radiolucency associated with an untreated cavity, osteonecrosis, changes in cortical bone, fragmented cancellous bone, and maxillary sinusitis [14]. The sclerotic tissue observed in the radiographic images may be caused by different reasons.

But the first and the most common and important reason is inflammation or infection, which can be simple osteomyelitis or MRONJ, and bone metastases are the second reason for it. The possibility of simple osteomyelitis or secondary to other reasons had been ruled out due to the lack of history of underlying diseases such as diabetes and the absence of periosteal reactions or mixed appearances in radiographic images (and not complete sclerosis). The possibility of the lesion being not metastatic is ruled out through three reasons:

First of all, she had no history of cancer. The second reason is the pattern of trabeculae in metastatic lesions which are more aggressive and much less diffuse than infections as well as they are located in one particular area. The third reason is unlike the unilateral lesion in this case, metastatic lesions are mostly Bilateral.

Multiple sclerosis (MS) is an autoimmune disease in which the immune system reacts by damaging the central nervous system (CNS components), especially myelin and oligodendrocytes. In fact, the immune system activates a reaction related to the formation of sclerotic plaques so that it would target different parts of CNS.MS is the most debilitating neurological disease in young adults, causing significant personal, social, and professional limitations. In patients with MS, there is a gradual and progressive limitation in functional skills, which eventually leads to disability. Clinical symptoms of MS include motor deficits, visual deficits, bulbar symptoms, cognitive impairments, and mental disorders that may interfere with oral and dental hygiene [15]

In addition, immunosuppressive drugs, which are used to slow down the progression of MS and manage the related symptoms which can also cause oral complications such as inflammation and overgrowth of gums, Candida infection, human papilloma virus infection, leukoplakia and according to recent evidence, they may be related to MRONJ. Other symptoms developed in MS patients include trigeminal neuralgia, numbness, muscle weakness, tremors, hemifacial spasm, dysphagia, and involuntary facial muscle contractions. [16]

The new strategies for this disease involve different kinds of treatments. B cells, involved in the activation of pro-

inflammatory T cells and the secretion of pro-inflammatory cytokines and the production of autoantibodies against myelin, play the major role in the pathogenesis of MS, so that the use of monoclonal antibodies which can destroy B cells as a treatment for autoimmune diseases has increased in recent years. As a result, anti-CD20 antibodies have been introduced as new treatments for MS. Previous results with rituximab, the first chimeric therapeutic anti-CD20 monoclonal antibody and B-cell destroyer that showed efficacy and effectiveness in MS clinical trials, encouraged researchers to evaluate the efficacy of an immunosuppressive drug containing a humanized anti-CD20 antibody named Ocrelizumab. this drug, launched in 2018, was the first drug to show effective effects in primary progressive MS (PPMS). [7, 16, 17] [8-10]

MRONJ has been proposed as a complication of anti-resorptive and anti-angiogenesis drugs, but so far it has not been reported as a complication of Ocrelizumab. But according to the articles, some cases of MRONJ have been reported due to the other immunosuppressive drugs such as Romosozumab, Adalimumab, Infliximab and Rituximab which are used to treat other autoimmune diseases, Due to cases of MRONJ as a result of the Rituximab (first chimeric anti-CD20 antibody) it seems that Ocrelizumab can cause MRONJ as well.

The reason for the diagnosis of MRONJ in this patient was the inexcusability of her clinical and radiographic findings along with medical and dental history to the other possible diagnoses. ON the examination of the patient's drug history, other drugs such as ibuprofen, baclofen, sertraline, and fampridine had a long history of consumption and it's so unlikely of them to cause MRONJ. It's obvious that MRONJ is a complication which occurs cumulatively and multi factorial, but this patient had no history of corticosteroids consumption in recent months, and the clinical symptoms of MRONJ developed right after a single injection of ocrelizumab.

It is also possible that the pain in the jaws of MS patients be interpreted as neuralgia secondary to MS disease by neurologists so that in many cases the real reason for pain and the diagnostic interpretation are not on the right track. In this patient, the diagnosis of neuralgia is ruled out through the patient's clinical symptoms like incomplete healing of socket of the extracted tooth, sclerosis in the jaw bone, ,the pattern of the pain, exudation from the area, severe sensitivity in touch and positive response to antibiotic treatment.

Since There is no cure for MRONJ, the best treatment is to prevent its occurrence. Primary prevention should be done not only before taking drugs related to MRONJ, but also during and after treatment to eliminate any possibility of this complication. It is the dentist's duty to accurately assess the risk factors leading to the development of MRONJ and to propose a strategy to eliminate these factors or minimize the risk.

The dentist should also emphasize the importance of effective dental hygiene, including regular check-ups for the patient. Maintaining oral health and early diagnosis of the disease is effective in reducing the prevalence of MRONJ, because if we diagnose MRONJ in its early stages, the probability of successful treatment increases.

At the same time, the delay in the diagnosis of MRONJ related to non anti-angiogenic drugs, which was mentioned in the present review, may be the reason for the exposure of necrotic bone in most of these cases.

Early diagnosis of MRONJ may increases the number of cases without bone exposure. On the other hand, osteonecrosis of the Jaw without exposure has been recognized recently and its definition remains a matter of debate among clinicians. [14] Studies a with larger number of patients using this drug are needed and recommended.

MRONJ worsens the quality of life related to oral health and prevents ideal dental treatment. It also may causes inability to chew and reduces daily activities due to the defects created in the jawbones after surgical treatment or in pathological progress. Therefore, it is necessary to clarify the exact mechanisms and create therapeutic strategies for MRONJ. [11]

Conclusion

In this article, a case of MRONJ is reported which may be caused by Ocrelizumab due to the fact that no other known risk factors or drugs were found in this patient to induce this complication except this drug to acknowledge MRONJ as a side effect of Ocrelizumab, more clinical studies must be conducted. In the end, it is necessary to mention that some of the new drugs may increase the possibility of MRONJ and should be prescribed more carefully to prevent the occurrence of this complication. It's possible to not only speed up the process of treatment and recovery but also improve the quality of life of the patient by early diagnosis of MRONJ.

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