



MANAGEMENT OF MEDICATION RELATED OSTEONECROSIS OF JAW - A CASE REPORT

Periodontology

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ABSTRACT

An uncommon and potentially serious adverse effect of anti resorptive and anti angiogenic drugs is Medication-related osteonecrosis of the jaw (MRONJ). In addition, to anti resorptive medications, MRONJ is now also reported to be associated with anticancer agents, including classic chemotherapy agents, angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), inhibitors of mammalian target of rapamycin, and immunotherapeutic agents. Clinical presentation includes gingival ulceration with exposed necrotic bone in the oral cavity involving either maxilla or mandible that has persisted for 6-8 weeks. And in severe cases it may cause spontaneous pain, tooth mobility, pathological fracture. However, MRONJ can be treated, and the likelihood of developing this condition can be reduced through prophylactic dental care and the maintenance of good oral hygiene. Dentists, as part of a multiprofessional team, have a critical role in preventing MRONJ. This article put forward a case report of rather uncommon presentation of necrosis of jaws associated with intake of anticancer drugs and intends to provide guidance for dental practitioners with regard to the screening, prophylactic treatment, diagnosis, and management of patients with this condition.

KEYWORDS

Medication related Osteonecrosis, Anticancer drugs, chemotherapy, prevention

Medication related osteonecrosis of jaw (MRONJ) has become a well-known side effect of bisphosphonate therapy which predominantly occurs in patients suffering from malignant diseases who receive intravenous administrations of nitrogen-containing bisphosphonates. More recently, similar problems have been described after treatment with other drugs used in chemotherapy.

Currently, medication-related ONJ (MRONJ) is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region for at least 8 weeks with a history of antiresorptive or antiangiogenic medication in the absence of radiation therapy to the jaws. The majority of ONJ cases occurred in the mandible (around 2/3 of the cases) with a predilection for the molar and premolar regions in both jaws. Besides exposed necrotic bone, pain and swelling of the surrounding soft tissues as well as intra- or extra-oral sinus tracts are typical signs of MRONJ. Furthermore, complications like abscess formation, pathological fractures, sinusitis and impairment of inferior alveolar nerve function might occur. The present study shows a case report of patient of MRONJ treated as conservatively as possible. Patient was managed with observation, oral antibacterial rinse, antibiotics and analgesics for pain control. After follow up of 12 months healing of the lesion was achieved and patient became symptom free.

Case Report

A 49 year old female patient reported with a complaint of pain and swelling in the right upper and lower posterior gum region. She also had fever of 1 week duration and submandibular tender lymph nodes. The pain was of two weeks duration and associated with slight swelling in the area. Her medical history was noteworthy for Carcinoma right breast and she had undergone modified radical mastectomy one year back. At the time of presentation, she had further undergone two cycles of chemotherapy including Adriamycin and cyclophosphamide. She had a history of Diabetes mellitus and was under treatment. There was no history of radiation therapy or intake of intravenous bisphosphonates.



Fig 1. Exposed bone covered with yellow slough that can be probed to bone, associated with infection

Intraorally, exposed bone covered with yellow slough on the buccal

gingiva in relation to upper right molars and lower left molars, and on the lingual aspect of lower right premolars were seen and overlying mucosa was erythematous. Severe tenderness on palpation of the right buccal vestibule in the area was noted. Intraoral clinical examination revealed surface ulceration with alveolar bone exposure on the alveolar ridge bilaterally. The patient had poor oral hygiene. The upper right second molar and lower right second molar, which exhibited Class I mobility and deep periodontal pocketing. The lower right second molar was tender to percussion and exhibited severe loss of alveolar bone on the distal aspect extending upto apical third with furcation radiolucency in PAN view taken. There was gingival erythema, minimal purulent drainage, and tenderness around the buccal and palatal areas of the exposed bone.



Fig 2. Healing at the end of two weeks

She was diagnosed with stage II ONJ of the right posterior maxilla, [16, 17 region] and mandible [45 region] and left posterior mandible [37, 38 region], owing to the presence of bone that could be clinically probed. After obtaining written consent from the concerned oncologist, the area was initially conservatively managed with oral prophylaxis and a course of antibiotic therapy. Augmentin 625mg for 7 days along with metronidazole 400mg for 3 days were given. The patient was advised to use 3% Hydrogen peroxide diluted with equal amounts of water as mouth rinse twice daily for one week. After the acute symptoms subsided, the tooth with poor prognosis were extracted. Following extraction, patient was kept under antibiotic cover, in addition to improved oral hygiene, local wound care with chlorhexidine, and routine nonsurgical oral prophylaxis. The area of exposed bone and root surface healed, and the patient has been symptom free at the follow up of one year.



Fig 3. One year follow up

DISCUSSION

An uncommon and potentially serious adverse effect of anti resorptive and anti angiogenic drugs is Medication-related osteonecrosis of the jaw (MRONJ). It can cause chronic pain, infection, dysfunction, and disfigurement and can affect the quality of life of affected individuals.² In most cases, a diagnosis of MRONJ requires the following

1. Current or previous treatment with bisphosphonates, denosumab, or antiangiogenic therapy
2. An area of exposed bone, or bone that can be probed through an intraoral or extraoral fistula and has persisted for greater than 8 week
3. No history of radiation therapy to the jaw or obvious metastatic disease of the jaw.³

Several professional associations have produced position papers to describe the clinical symptoms, radiographic findings, and recommended management of patients with ONJ.⁴ The AAOMS has defined the stages of MRONJ to describe disease presentation and to facilitate the appropriate stratification of patients:

Stage 0—no clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms

Stage 1—exposed and necrotic bone/fistulae that can be probed to bone, asymptomatic, no evidence of infection

Stage 2—exposed and necrotic bone/fistulae that can be probed to bone, associated with infection

Stage 3—exposed and necrotic bone/fistulae that can be probed to bone, associated with infection and additional complications³

In addition, to anti resorptive medications, MRONJ is now also reported to be associated with anticancer agents, including classic chemotherapy agents, angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), inhibitors of mammalian target of rapamycin, and immunotherapeutic agents.

Several possible pathogenic mechanisms including over-suppression of jawbone turnover, specific pathogens, antiangiogenic effects, and soft tissue toxicity have been proposed to be the main drivers of the disease. While the precise etiology is still under current investigation, it is now widely accepted that medication-related osteonecrosis of the jaw has a multifactorial etiology.¹

The importance of localized dental and periodontal infection in the development of MRONJ has been highlighted in recent animal experiments, which supported the findings from radiologic, histologic, microbiologic, and clinical studies.⁵ Furthermore, evidence is emerging which suggests that infections of dental and periodontal origin may precede the appearance of necrotic bone.⁶ Dentists, thus may be one among the first to recognize such symptoms in patient and should be capable of timely diagnosis of MRONJ.

In recognition of this, American Society of Clinical Oncology and Cancer Care Ontario made the following recommendation: "A dental assessment is recommended, where feasible, before commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with before starting treatment, if possible." As MRONJ is now associated with other medications as well, a thorough dental check up of patients are recommended before, during as well as after chemotherapy. Also, several other factors have also been associated with an increased risk of MRONJ, including smoking; poor oral hygiene; and comorbidities, such as anemia, diabetes mellitus, and renal failure.³

In the present case patient had undergone two cycles of chemotherapy involving adriamycin and cyclophosphamide. Case reports of incidence of MRONJ as a side effect of these anticancer drugs are rare in literature.⁷ The stage of MRONJ at presentation is prognostic for the success of conservative (nonsurgical) treatment, with only a very low likelihood of healing in patients who have higher stages of the disease.⁸ In 2007 and 2009, the American Association of Oral and Maxillofacial Surgery (AAOMS) published stage-specific treatment recommendations for BRONJ which are still up to date. Summarized, conservative treatment of BRONJ stages 0 and I, superficial debridement of stage II, and debridement stage III is recommended.¹ It is the dentist who will have to decide if and when to initiate treatment with chlorhexidine or broad-spectrum antibiotics.

During the interval between the diagnosis and the appointment with the OMFS, antibacterial rinses can be started as soon as MRONJ is suspected, but antibiotics should be prescribed only when signs of infection are observed.¹ In this case, antibacterial mouth rinses were given to the patient and local wound care procedures done along with antibiotic therapy prior to the referral to OMFS department.

CONCLUSION

Dentists of patients receiving medications at risk of MRONJ have a pivotal role in the prevention and early diagnosis of MRONJ.³ The number of cancer and non-cancer patients being treated with ONJ-related drugs and, therefore, the number of potentially side effects seem constantly on the increase, also on the light of new drugs related to ONJ. As there are reports emerging of necrotic exposed bone in the oral cavity, i. e.; symptoms similar to MRONJ, in patients treated with other medications, other than bisphosphonates, including steroids, methotrexate, and chemotherapeutics, or as a result of infection, coagulation disorders, or trauma, it may be prudent to report and compare these findings to identify a new population of potentially at-risk patients for whom preventative measures can be taken. To optimize the use of these agents in practice and to ensure appropriate focus on the risk of MRONJ, and improve the patient's quality of life, a multidisciplinary approach with sustained dialogue and good collaboration is required among dentists, physicians, oral oncologists, OMFSs, and other health care professionals involved in a patient's care.

At present, panoramic radiographs can be considered as a primary modality for MRONJ imaging. In the future, nuclear medicine imaging like combined SPECT/CT or PET/CT may further improve the diagnosis of MRONJ by combining functional and anatomical information.¹

Even though conservative treatment have shown to slow down disease progression and alleviate super infection of the exposed bone, surgical treatment protocols have shown superior results. The fluorescence-guided bone resection is an innovative and promising treatment modality. Extensive surgery should only be applied in special cases respecting the surgeons' experience and extent of MRONJ of the patient. The adjuvant treatments, such as hyperbaric oxygen therapy, low-level laser applications and laser surgery, can help to reduce the antibiotic cycles and improve clinical results potentially.¹

Risk reduction measures in the cancer setting would include provision of prophylactic dentistry before the start of bisphosphonate therapy, including restorative dental treatment and extraction of non-restorable dentition. In those instances where dental extractions cannot be avoided, there are no clear indications of effective risk-reduction measures. Meticulous dental examination and special precautions in the performance of dentoalveolar surgeries like an atraumatic extraction technique have to be provided for patients prior to treatment or in active treatment with the mentioned drugs to reduce risk of ONJ development.³ As evidenced by the present case report, there is also an urgent need to define the characteristics of the increasingly reported cases of osteonecrosis of the jaw related to medications without known antiresorptive properties.

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