Oral Bisphosphonates — Spontaneous Osteonecrosis of the Jaw

Hajer Abdulhafid Derbi and Gelsomina L. Borromeo
Department of Dentistry, University of Melbourne, Australia

Abstract
This report documents a case of bisphosphonate-related osteonecrosis of the jaw (MRONJ) in an osteoporotic 75-year-old female residing in a nursing home who underwent 70 mg of alendronate weekly for five years followed by 35 mg risedronate weekly. In 2012, she was diagnosed with a painless extrarctal draining sinus below the right border of the mandible. Furthermore, the right lower lip and chin were numb. She underwent several courses of antibiotics to no avail. Two years later, the patient was referred to the domiciliary service at Royal Dental Hospital Melbourne, Victoria. An area of infected, exposed necrotic bone at the region of 46 and 47 with active suppuration was noted. A panoramic radiograph showed opacity in quadrant four with scalloping and bone sequestration of the superior border of the alveolus. Bone exposure persisted for 8 weeks (Stage III MRONJ). The patient had poor oral health, potentially exacerbating the MRONJ. She was unsuccessfully managed using a combination of oral debridement and sequestrectomy. The potential role of infection in MRONJ is still debated, and greater attention should be paid to the role of adequate long-term oral hygiene protocols as part of overall management. A collaborative effort between dentists and physicians in deciding on the patient’s dental treatment is also recommended.

ABBREVIATIONS
MRONJ: Medication-Related Osteonecrosis of the Jaw; CTX: Cross-Linked telopeptide of Type 1 Collagen; ONJ: Osteonecrosis of the Jaw; ASBMR: American Society for Bone and Mineral Research; AAOMS: The American Association of Oral and Maxillofacial Surgeons

INTRODUCTION
Since initial reports [1-4] of cases with osteonecrosis of the jaw (ONJ) associated with bisphosphonate use, there has been considerable interest in this variant of jaw necrosis. Bisphosphonate (BP)-associated ONJ or medication-related osteonecrosis of the jaw (MRONJ) was formalised by the American Society for Bone and Mineral Research (ASBMR) and recently updated by The American Association of Oral and Maxillofacial Surgeons (AAOMS) as a non-healing area of exposed bone or bone that can be probed through an intraoral or extrarctal fistula in the maxillofacial region present for more than 8 weeks, in a patient who was receiving or had been exposed to an antiresorptive or antiangiogenic agent and in whom the jaw had not been irradiated or subject to metastatic disease [5]. It has been documented that the prevalence of ONJ with intravenous nitrogen-containing bisphosphonate is significantly higher than that seen with oral bisphosphonates [6-8], which is also linked to the duration of exposure and number of infusion [6-8]. The current estimated prevalence of ONJ among oral bisphosphonate-treated populations has ranged from 0.001% to 0.01% [9, 10]. Even among the oral formulations of these drugs, differences exist in the risk of MRONJ. Alendronate seems to have a greater affinity for bone tissues compared to other oral bisphosphonates, is more potent, and, most importantly, is more readily prescribed, resulting in it being a more frequent MRONJ-causing oral agent [8].

CASE PRESENTATION
A 75-year-old woman residing in a local aged care residential facility was referred to the domiciliary service at Royal Dental Hospital Melbourne in December 2014. She presented with a history of a painless cutaneous draining sinus below the right body of the mandible. Bisphosphonate (BP)-associated ONJ or medication-related osteonecrosis of the jaw (MRONJ) was formalised by the American Society for Bone and Mineral Research (ASBMR) and recently updated by The American Association of Oral and Maxillofacial Surgeons (AAOMS) as a non-healing area of exposed bone or bone that can be probed through an intraoral or extrarctal fistula in the maxillofacial region present for more than 8 weeks, in a patient who was receiving or had been exposed to an antiresorptive or antiangiogenic agent and in whom the jaw had not been irradiated or subject to metastatic disease [5]. It has been documented that the prevalence of ONJ with intravenous nitrogen-containing bisphosphonate is significantly higher than that seen with oral bisphosphonates [6-8], which is also linked to the duration of exposure and number of infusion [6-8]. The current estimated prevalence of ONJ among oral bisphosphonate-treated populations has ranged from 0.001% to 0.01% [9, 10]. Even among the oral formulations of these drugs, differences exist in the risk of MRONJ. Alendronate seems to have a greater affinity for bone tissues compared to other oral bisphosphonates, is more potent, and, most importantly, is more readily prescribed, resulting in it being a more frequent MRONJ-causing oral agent [8].

The patient suffered from osteoporosis, and had been treated with 70 mg of alendronate weekly for five years followed by 35 mg risedronate weekly. Since 2012, she began to complain of a painful cheek swelling on the right side of her face with an accompanying salty taste. The patient received several courses of antibiotics including amoxicillin and metronidazole tablets with no symptomatic relief.
A clinical examination revealed an extraoral fistula under the right body of the mandible and a 1.5 cm diameter area of exposed necrotic bone at the region of the first and second molars associated with mucosal inflammation and purulent discharge (Figure 3). She had neglected oral health with poor oral hygiene and generalized severe gingivitis. Traumatic fibroepithelial polyps were noticed and confirmed by biopsies on the tip and left lateral border of her tongue.

The patient underwent panoramic radiography (Figure 4A) and CBCT, which revealed radiopacity of the bone in quadrant four with scalloping and a bone sequestration of the superior border of the alveolus. The lesion fulfilled the criteria for diagnosis as Stage III MRONJ with a significant risk of pathological fracture. This had been managed by debridement including sequestrectomy and dental extraction of teeth on the affected side. The neck of the sinus healed together with the associated MRONJ and draining sinus (Figure 4B). However, five months later, on examination, purulent discharge was noticed at the 48 region without any exposed open or radiographic change, thereby fulfilling three criteria for a diagnosis of Stage 0 MRONJ. This subsequently healed after administration of amoxicillin 500mg, three times a day for five days but only in conjunction with rigorous improvements in her oral hygiene. This included several sessions where deep scaling and root debridement took place together with oral home care consisting of using 0.12% chlorhexidine mouthwash three times a day and regular tooth brushing with fluoridated toothpaste twice a day. After healing of the MRONJ, six teeth required extraction due to poor prognosis and all had shown good healing with no reoccurrence of MRONJ.

**DISCUSSION**

The most common trigger for MRONJ is dental extraction, with the mandible more frequently involved due to the rate of bone turnover is greater compared to the maxilla, or in both jaws [9]. A number of risk factors have been associated with the development of MRONJ, including advanced age, steroid therapy, compromised health [7, 8] periodontal disease [11], implant placement, denture use [2, 12] and underlying systemic condition for which the patient prescribed BP for [7, 13]. Interestingly, the MRONJ, six teeth required extraction due to poor prognosis and all had shown good healing with no reoccurrence of MRONJ.
25% of cases of IV MRONJ are classified as spontaneous [14], although many researchers hypothesize that an untreated, non-restorable carious or abscessed dentition and/or the presence of widened periodontal ligaments [15], may be the undetectable predisposing factors that are responsible. This was certainly possible in the current case.

Several studies [16-18] have reported cases of non-exposed MRONJ, especially in its early stages, in patients with a history of bisphosphonate use. In these patients, although exposed bone was not present, purulent drainage with or without sinus tracts, the presence of deep periodontal pockets, swelling, and pain were common clinical findings [16-18]. This was similar to the second presentation of the MRONJ in this case.

After treating the MRONJ and the underlying poor periodontal health and improving overall oral health, the patient had multiple six upper and lower teeth extracted with no complications. In addition, Chlorhexidine gluconate (0.12 %) mouthwash and amoxicillin (1 gram) were prescribed to be used prior to the extractions together with 500 mg amoxicillin three times a day for five days after the procedure. Whilst there is no literature stating the most suitable antibiotic protocol in such cases, this regime was shown to be of benefit in this and other cases managed for MRONJ [17].

There is considerable debate regarding the use of bone turnover marker carboxyl-terminal cross-linked telopeptide of type 1 collagen (beta-CTX-1) to predict ONJ risk. The possibility of using CTX was first suggested by Marx [14]. It was proposed that the levels of serum CTX may predict the subsequent risk of developing osteonecrosis of the jaws (ONJ) after oral surgery procedures for patients taking oral (BPs) [14]. Many authors have questioned and even refuted the use of CTX as a predictive biomarker for ONJ [7,8,15,19-23]. This is mainly attributed to differences between fasting and non-fasting states, intermittent variability, and non-standardized laboratory reference ranges. In addition, this unproven preoperative assessment tool is not cost effective and unnecessarily increases healthcare spending. Therefore, although low CTX is a reflection of recent antiresorptive treatment, current data do not support it as having a useful role in predicting the risk of ONJ. In the current case, CTX was not used to predict MRONJ risk prior to dental extractions. The poor prognosis of the teeth meant that extraction was essential.

There is also debate and inconsistency about whether discontinuing oral BP therapy before surgery will decrease the chances of developing ONJ after an oral surgery procedure. According to The Canadian Association of Oral and Maxillofacial Surgeons [24], a consideration of interruption of oral bisphosphonate therapy for a patient with osteoporosis several months prior to a dental procedure and throughout the healing period may be considered. The American Association of Oral and Maxillofacial Surgeons on the other hand advise cessation three months prior to invasive dental procedures only when the duration of therapy exceeds 4 years. This time frame may be shortened in the presence of certain comorbidities, such as acromic corticosteroid or antiangiogenic use. The American Dental Association Guidelines recognised the lower risk in osteoporosis patients, and stated that the discontinuation of oral BP was not necessary prior to dental procedures [25]. Hence it is clear that confusion exists as to what should formulate best practice which has been seen in other aspects associated with ONJ and bisphosphonate use [7].

For oncology patients receiving IV bisphosphonates, several authors considered interruption of the bisphosphonate for 3 to 6 months prior to the procedure, and until the surgical site has healed [26], others considered ceased the BP at least one month prior to invasive procedures and not commenced until healing achieved [7], for an urgent invasive dental procedure, it is recommended that the procedure be completed and interruption of bisphosphonate therapy be considered during the healing period, if the medical condition permits [26].

As bisphosphonates have long-term skeletal retention and hence if a patient has a serum CTX value less than 150 pg/mL, they are considered within the therapeutic range of BP therapy to reduce the incidence of skeletal fractures [27]. A drug holiday may have the potential to move the patient out of the therapeutic range thereby, as the gold standard of antiresorptive therapy is fracture reduction. This indicates the importance of determining which patients are at a higher risk of experiencing fractures before discontinuing BP therapy. The association of hip fracture with high mortality is also an important consideration especially in elderly patients [28]. As there is little evidence to support the discontinuous of BP in terms of changing the outcome of adental procedure, taken together with the increased fracture risk in an elderly patient residing in a residential aged care facility, oral risendronate was not discontinued for the lady in the case report.

Management of MRONJ is both challenging and controversial. Stage III can be managed successfully following the AAOMS protocol including debridement, resection, in combination with antibiotic therapy; however, patients with stage III MRONJ may require resection and immediate reconstruction. Teriparatide has been approved for osteoporosis management [29] with several case reports have disclosed favourable therapeutic outcomes from using it in managing MRONJ, which might be new hope especially in elderly people where mandibulectomy is not practical [30-33].

REFERENCES


