New bone formation in the mandibular corpus after mucosal healing in a patient with medication related osteonecrosis of the jaw after treatment by bisphosphonates for multiple myeloma: a case report and pictorial review

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Abstract

Objective: First cases of osteonecrosis of the jaw in patient exposed to bisphosphonates were presented in 2003. Bisphosphonates related osteonecrosis of the jaw (BRONJ) was further extended to medication-related osteonecrosis of the jaw (MRONJ) to include antiresorptive and anti-angiogenic drugs. Some directives were described for the treatment of this disease in function of its gravity. Treatments of high stage of MRONJ are subject to discussion because of their morbidity. Complete healing is difficult to reach and often needs combination of invasive and non-invasive treatment.

Case report: We report and illustrate a clinical case of new bone formation after MRONJ on pamidronate and zoledronate treatment for multiple myeloma. The treatment of choice was sequestrectomy and conservative treatment.

Discussion: The consensus to reach a complete healing after MRONJ is not already known. More studies are needed.

Keywords: Medication related osteonecrosis of the jaw, MRONJ, antiresorptive drugs, bisphosphonate, new bone formation
Introduction

Both the intravenous (IV) and oral types of bisphosphonates (BPs) and other antiresorptive drugs (ARDs) are now commonly prescribed to treat osteoporosis, bone resorption related to metastatic tumours to the bone or osteolytic lesions of multiple myeloma [1, 2]. Osteolytic lesions and primary hyperparathyroidism are the main causes of hypercalcemia managed by ARDs. ARDs do not improve cancer specific survival, but have a significant positive effect on the quality of life for patient with advanced cancer involving the skeleton.

In 2014, the American Association of oral and Maxillofacial Surgeons (AAOMS) defined medication-related osteonecrosis of the jaw (MRONJ) to encompass BPs and other ARDs. MRONJ is an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after its identification by a healthcare provider in a patient who is receiving or received ARDs and who has not had radiation therapy to the cervical-craniofacial region [3].

In 2014, Ruggiero et al. proposed a classification of MRONJ in five stages. This classification is based on patient (ARDs treatment, symptoms), clinical observation and on radiological examination. The treatment of MRONJ is based on this classification [3]. Because of the difficulty to understand this disease and the role of ARDs, discussion is still open between non-invasive and surgical treatment.

Case report

A 75-year-old male patient was referred to our department with pain to the mandible for two years. The patient had never seen a dentist or a general practitioner since two years. The patient was treated by pamidronate (Aredia®) followed by zoledronate (Zometa®) for a multiple myeloma for four years. The patient never received information about dental healthcare in relation with ARDs prescription. At the first consultation, the diagnosis of MRONJ was performed because of the long duration of exposed bone on the left corpus of the mandible. The MRONJ was classified stage 3 because of the extension of the lesion to the inferior border of the mandible (Figures 1, 2).
Fig. 1. Panoramic X-ray of the osteonecrosis of the left mandibular corpus (August 2018). Arrows and dotted line: limits of the osteonecrosis. Dashed arrow: osteosclerosis of the surrounding bone with lack of trabeculation when compared with the right side.

Fig. 2. CT scan of the osteonecrosis of the left mandibular corpus (August 2018). Two-dimensional coronal views through the left mandibular corpus. A-C: osteolytic lesion of the alveolar bone with osteosclerotic surrounding bone (arrows). D-L: sequestration of the alveolar bone (dashed arrows).
The treatment at the first consultation was an atraumatic removing of necrotic bone, and the prescription of a mouth wash with chlorhexidine, three times a day. Follow-up was performed every month. After 4 months of this treatment, no improvement of the MRONJ was detected and oral penicillin was given because of pain and spontaneous discharge of purulent material. The dose of penicillin was 1gr, 2 times a day during 2 weeks. Two months later, small sequestrectomy was achieved without local anaesthesia, and the biopsy was sent to the pathologist. Necrotic bone colonized by actinomyces was identified. The BPs treatment was stopped by the oncologist due to MRONJ. No pain was described by the patient and he acquired a good quality of life. However, the patient presented himself 7 months later, and an intensive sequestrectomy was performed at that time under local anaesthesia (mepivacaïn without adrenaline). This was performed because of mobile bone. No wound closure was needed because of spontaneous healing of mucosa below the necrotic bone. Penicillin was prescribed for a long period of time. During 8 months, patient received oral penicillin (Amoxicillin® 1 gr, 2 times a day) because of the presence of actinomyces and of recurrent disease. After this treatment, clinical examination showed a complete healing of the gingiva and the patient was pain-free (Figure 3).

![Fig. 3. Panoramic X-ray after sequestrectomy (April 2019). * Bone area after sequestrectomy in the posterior and left mandibular corpus. Arrows: osteonecrosis on the anterior left mandibular corpus. Teeth n°32, and 33 are missing.](image)

The patient came back to our department three years later for painful MRONJ of the upper right maxilla. Follow-up during 3 years after sequestrectomy was organized but patient did not show up. In relation with his MRONJ, a panoramic X-rays and a maxillofacial CT scan were performed to evaluate this new outbreak of MRONJ. The panoramic X-Rays and the CT scan showed complete ossification of the left corpus of the lower mandible (Figures 4, 5).
Fig. 4. Panoramic X-ray after three years (April 2022). Arrows: new bone formation in all the left mandibular corpus and in the area of the sequestrectomy.

Fig. 5. CT-scan of new bone formation after three years (April 2022). A-K: coronal view through left mandibular bone. A-G: osteosclerosis (arrows). G-K: bone neo-formation with presence of trabecular bone (dotted arrows).
Discussion

Many hypotheses exist about the relation between ARDs and MRONJ. Some authors proposed that MRONJ is related to a poor bone turnover [2]. The inhibition of bone remodelling and angiogenesis impairs the regenerative capacity of bone [4, 5]. This, in combination with infection, other drugs (chemotherapy, steroids, disease-modifying antirheumatic drugs), pre-existing diseases (diabetes, rheumatoid arthritis), compromised immune response, and dentoalveolar trauma may lead to MRONJ [3,4].

The prevalence of MRONJ for sequential pamidronate/zoledronate therapy is 19% [6]. For cancer treatment, with sequential bisphosphonates/denosumab therapy, the prevalence is 13% while it is 5% for IV BPs alone, and 4% for denosumab alone [6].

Computed tomography (CT) without contrast appears to be the best radiological examination method for MRONJ diagnosis and treatment because of its good availability and the assessment of the soft tissues [7]. It is useful for the diagnosis of extended necrosis, and to plan the resection and further bone reconstruction [7].

Cone beam CT (CBCT) could be an alternative for bone imaging with lower radiation [7]. We choose the combination of routine panoramic X-Ray and CT scan for the follow-up of the patient (as the CBCT was not available in our hospital) [7].

Ruggiero et al., described in 2014 and modified in 2022 the classification for patients who presented with MRONJ [3] (Table 1).

Table 1. Ruggiero classification of patients with MRONJ.

<table>
<thead>
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<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>« Patient at risk »</td>
<td>Patient who received ARDs without necrotic bone</td>
</tr>
<tr>
<td>0</td>
<td>No clinical evidence of necrotic bone but symptoms, radiological changes or non-specific clinical discovery</td>
</tr>
<tr>
<td>I</td>
<td>Necrotic bone or fistulisation in patient with no symptoms and no infection</td>
</tr>
<tr>
<td>II</td>
<td>Necrosing bone or fistulisation with pain or erythema with or without infection</td>
</tr>
<tr>
<td>III</td>
<td>Necrosing bone or fistulisation with pain, infection and at least one of the following characteristics: necrosing bone which extends beyond the alveolar bone, pathological fracture, oral cavity-mouth-nasal or oral cavity-sinus communication or osteolysis that extends to the lower border of the jaw or to the sinusal floor.</td>
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The treatment of the earlier stages (0, I) is based on medical management (mouthwash with chlorhexidine, antibiotics) [3]. The treatment of the advanced stages (III, IV) is a combination of medical and surgical approach [3]. Because this disease impairs the quality of life, it is important to find the good way to help the patient. In 2020, based on a systematic review, Vanpoeccke et al, concluded that for all other stages (I, II) of MRONJ, the best way to help the patient is based on antibiotics, antiseptic mouthwash, and on periodical dental check-ups [8]. For the
Stage III, conservative treatment alone was insufficient for achieving the full mucosal healing [8]. The best treatment for MRONJ at the stage III was an extensive bone resection up to the viable bleeding margins with or without microvascular flap reconstruction [8]. Conservative treatment alone could be recommended for patient who are ineligible for surgery [8]. In our case, a complete mucosal healing and bone remodelling was achieved with conservative surgical treatment (sequestrectomy) alone [8].

In 2015, Khan et al., [9] described that an alternative of conservative therapy must be chosen if there is an obvious progression of the disease such as uncontrolled pain during conservative treatment, or for a patient for whom the oncologist must discontinue ARD because of osteonecrosis of the jaw [9]. Conservative treatment is based on antibiotics and mouthwash. In MRONJ, the majority of the infections are based on Actinomyces which is a Gram positive, filamentous, facultative and anaerobic bacterium that exists in the normal flora of oral cavity, gastrointestinal tract and in female genital tract [10]. A lot of studies were performed about which antibiotics are the best to eradicate Actinomyces [10]. Kaplan et al., described the improvement of symptoms with clinical evolution after treatment of MRONJ with Actinomyces with long time penicillin treatment [10, 11]. Valour et al., recommended high doses of penicillin G or amoxicillin during 6 to 12 months [12]. Penicillin G or amoxicillin are considered drugs of choice for the treatment of actinomycosis [12]. Third-generation cephalosporins are considered to be active on A. israelii but are less frequently used [12]. Piperacillin–tazobactam, imipenem, and meropenem are active, but the risk of acquisition of resistant bacteria must limit the use of these large-spectrum antibiotics to few severe cases [12]. The choice between povidone iodine or chlorhexidine (CHX) as a mouthwash is still discussed [13]. Hadaya et al., preferred toothbrush dipped in CHX than a mouthwash alone to remove all plaque and debris from the exposed bone [14]. Due to the high morbidity of MRONJ, a lot of new treatments must be explored [15]. The use of low-level laser therapy, ozone, hyperbaric oxygen, mesenchymal stem cell-based therapy shows good result at least but these treatments are not sufficient alone [15]. Only teriparatide alone should be efficient but more studies about this drug are needed and no consensus are published yet. The incidence of osteosarcoma after teriparatide treatment is not negligible. For Watanabe et al., 9 males rats and 2 females rats developed osteosarcoma after 2 years of treatment (total population of the study consisted of 55 rats) [15,19].

In our case report, complete wound healing was achieved below the sequestrectomy. An hypothesis of this wound healing is that sequester could isolate the mucosa from the oral cavity. A combination with mouthwash, antibiotics and isolated mucosa could lead to healing. It is important to obtain this wound healing because of the risk of the exposition of bone to the oral microbiome [16]. Often, there is no wound healing and local or distant flaps are needed. This is due to ARD that impacts the mucosa too. BPs have also been associated with decreased cell proliferation and induction of apoptosis in keratinocytes and fibroblasts resulting in impaired healing.
and wound differentiation [16].

Description of wound healing of the mandible after MRONJ with IV or oral ARDs application has been already published and a systematic review was conducted but with no history of a complete bone healing [17]. In 2015, Wehrhan et al., found that the bone remodelling is related to Msx1 and DL-5 genes expression [18]. Msx1 stimulates osteoblast proliferation [18]. BPs inhibits Msx-1 expression [18]. When BPs are stopped for more than their half-life, the expression of Msx-1 may increase, and conduct to new bone formation [18]. The explanation of no more MRONJ is elucidated but the new formation of the bone is not yet completely understood [17]. Stage III of MRONJ is a challenge for maxillofacial surgeon because of the high morbidity of this disease. Conservative treatment (mouthwashes and antibiotherapy) is the basis of MRONJ treatment but surgical treatment is often needed. Sequestrectomy appears to be a good treatment and allows to avoid flap reconstruction if mucosal healing is found under the sequester. Even if there is a lot of publication about MRONJ, no consensus is reached yet, and more studies are needed about new therapies. The take-home message in relation with MRONJ is the importance of carry out oral examination before starting ARD treatment, and to perform dental follow-up during and after this treatment.
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Ethical approval: there was no need for ethical committee approval for this case report

Informed consent: an oral consent was obtained from the patient but no written consent was obtained before the death of the patient. The patient had no family. All images were anonymized and no private data were provided allowing the patient’s identification.

Authors contribution:

<table>
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<th>Author</th>
<th>Contributor role</th>
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<tr>
<td>Maxime Debiève</td>
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References


4. Ficarra G, Beninati F. Bisphosphonate-related osteonecrosis of the jaws: an


