



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

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20 Disclaimer: the views expressed in the submitted article are our own and not an of-
21 ficial position of the institution or funder.
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Abstract

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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

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45 Introduction

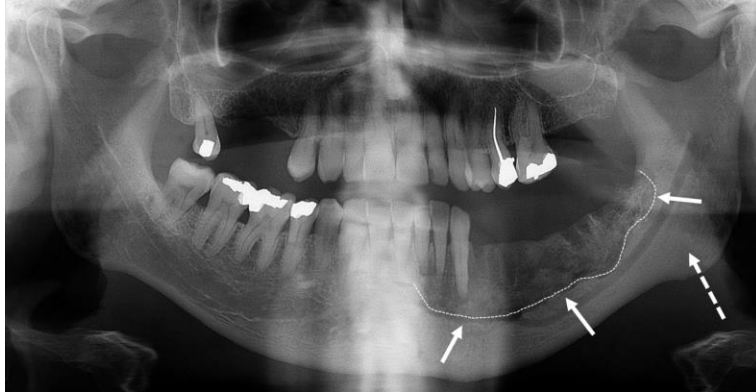
46 Both the intravenous (IV) and oral types of bisphosphonates (BPs) and other
47 antiresorptive drugs (ARDs) are now commonly prescribed to treat osteoporosis,
48 bone resorption related to metastatic tumours to the bone or osteolytic lesions of
49 multiple myeloma [1, 2]. Osteolytic lesions and primary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

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

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

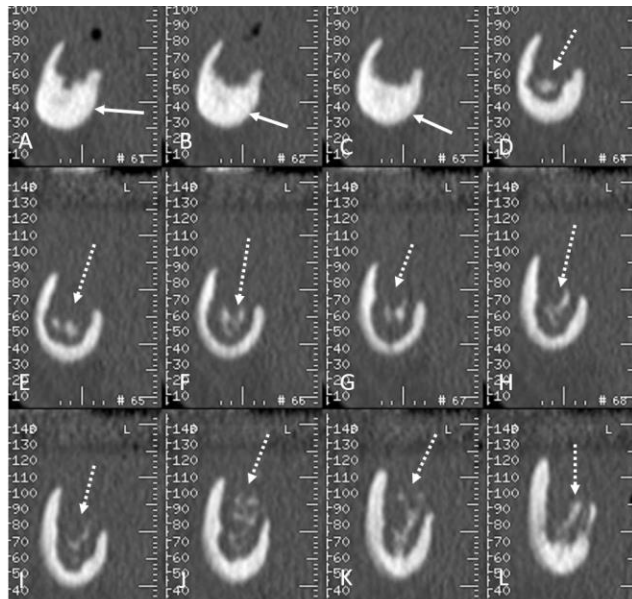
64 Case report

65 A 75-year-old male patient was referred to our department with pain to the
66 mandible for two years. The patient had never seen a dentist or a general practitioner
67 since two years. The patient was treated by pamidronate (Aredia®) followed by
68 zoledronate (Zometa®) for a multiple myeloma for four years. The patient never
69 received information about dental healthcare in relation with ARDs prescription. At
70 the first consultation, the diagnosis of MRONJ was performed because of the long
71 duration of exposed bone on the left corpus of the mandible. The MRONJ was
72 classified stage 3 because of the extension of the lesion to the inferior border of the
73 mandible (Figures 1, 2).
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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.



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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).

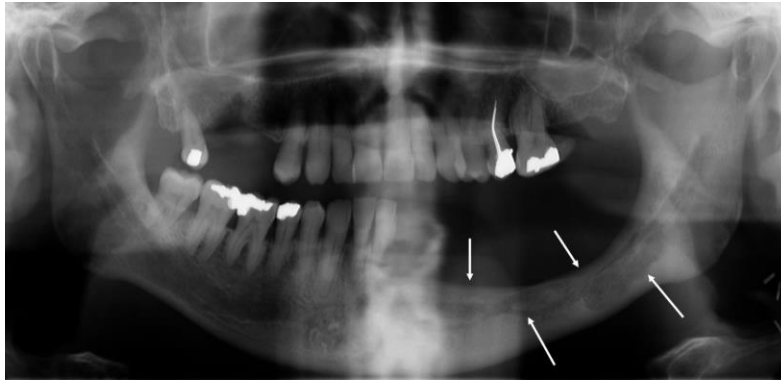
89 The treatment at the first consultation was an atraumatic removing of necrotic bone,
90 and the prescription of a mouth wash with chlorhexidine, three times a day. Follow-
91 up was performed every month. After 4 months of this treatment, no improvement of
92 the MRONJ was detected and oral penicillin was given because of pain and
93 spontaneous discharge of purulent material. The dose of penicillin was 1 gr, 2 times a
94 day during 2 weeks. Two months later, small sequestrectomy was achieved without
95 local anaesthesia, and the biopsy was sent to the pathologist. Necrotic bone
96 colonized by actinomyces was identified. The BPs treatment was stopped by the
97 oncologist due to MRONJ. No pain was described by the patient and he acquired a
98 good quality of life. However, the patient presented himself 7 months later, and an
99 intensive sequestrectomy was performed at that time under local anaesthesia
100 (mépivacaïn without adrenaline). This was performed because of mobile bone. No
101 wound closure was needed because of spontaneous healing of mucosa below the
102 necrotic bone. Penicillin was prescribed for a long period of time. During 8 months,
103 patient received oral penicillin (Amoxicillin® 1 gr, 2 times a day) because of the
104 presence of actinomyces and of recurrent disease. After this treatment, clinical
105 examination showed a complete healing of the gingiva and the patient was pain-free
106 (Figure 3).
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109 **Fig. 3.** Panoramic X-ray after sequestrectomy (April 2019). * Bone area after
110 sequestrectomy in the posterior and left mandibular corpus. Arrows:
111 osteonecrosis on the anterior left mandibular corpus. Teeth n°32, and 33 are
112 missing.
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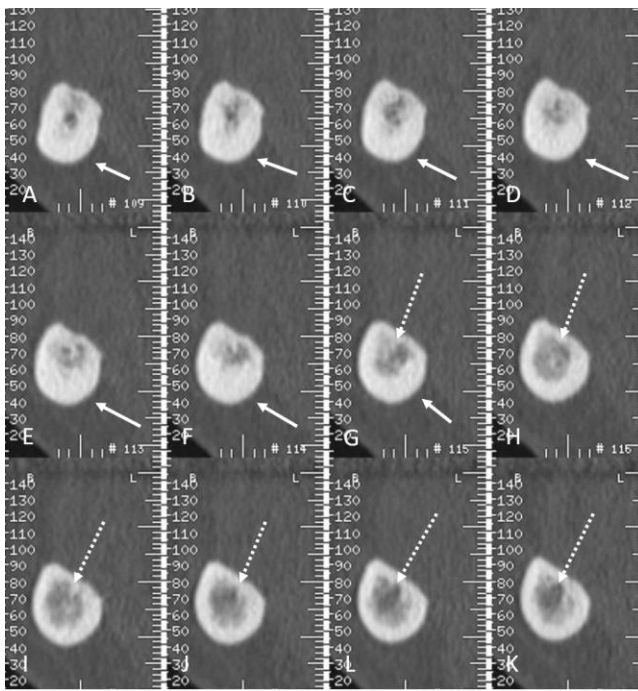
114 The patient came back to our department three years later for painful MRONJ of the
115 upper right maxilla. Follow-up during 3 years after sequestrectomy was organized
116 but patient did not show up. In relation with his MRONJ, a panoramic X-rays and a
117 maxillofacial CT scan were performed to evaluate this new outbreak of MRONJ.
118 The panoramic X-Rays and the CT scan showed complete ossification of the left
119 corpus of the lower mandible (Figures 4, 5).

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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.



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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).

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Discussion

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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.

Stage	Description
« Patient at risk »	Patient who received ARDs without necrotic bone
0	No clinical evidence of necrotic bone but symptoms, radiological changes or non-specific clinical discovery
I	Necrotic bone or fistulisation in patient with no symptoms and no infection
II	Necrosing bone or fistulisation with pain or erythema with or without infection
III	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.

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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, Vanpoecke 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

161 stage III, conservative treatment alone was insufficient for achieving the full
162 mucosal healing [8].

163 The best treatment for MRONJ at the stage III was an extensive bone resection up to
164 the viable bleeding margins with or without microvascular flap reconstruction [8].
165 Conservative treatment alone could be recommended for patient who are ineligible
166 for surgery [8].

167 In our case, a complete mucosal healing and bone remodelling was achieved with
168 conservative surgical treatment (sequestrectomy) alone [8].

169 In 2015, Khan et al., [9] described that an alternative of conservative therapy must
170 be chosen if there is an obvious progression of the disease such as uncontrolled pain
171 during conservative treatment, or for a patient for whom the oncologist must
172 discontinue ARD because of osteonecrosis of the jaw [9].

173 Conservative treatment is based on antibiotics and mouthwash. In MRONJ, the
174 majority of the infections are based on Actinomyces which is a Gram positive,
175 filamentous, facultative and anaerobic bacterium that exists in the normal flora of
176 oral cavity, gastrointestinal tract and in female genital tract [10]. A lot of studies
177 were performed about which antibiotics are the best to eradicate Actinomyces [10].
178 Kaplan et al., described the improvement of symptoms with clinical evolution after
179 treatment of MRONJ with Actinomyces with long time penicillin treatment [10, 11].
180 Valour et al., recommended high doses of penicillin G or amoxicillin during 6 to 12
181 months [12]. Penicillin G or amoxicillin are considered drugs of choice for the
182 treatment of actinomycosis [12]. Third-generation cephalosporins are considered to
183 be active on *A. israeli* but are less frequently used [12]. Piperacillin–tazobactam,
184 imipenem, and meropenem are active, but the risk of acquisition of resistant bacteria
185 must limit the use of these large-spectrum antibiotics to few severe cases [12].

186 The choice between povidone iodine or chlorhexidine (CHX) as a mouthwash is still
187 discussed [13]. The CHX appears to be the most used because of its cationic nature
188 [13]. Hadaya et al., preferred toothbrush dipped in CHX than a mouthwash alone to
189 remove all plaque and debris from the exposed bone [14].

190 Due to the high morbidity of MRONJ, a lot of new treatments must be explored
191 [15]. The use of low-level laser therapy, ozone, hyperbaric oxygen, mesenchymal
192 stem cell-based therapy shows good result at least but these treatments are not
193 sufficient alone [15]. Only teriparatide alone should be efficient but more studies
194 about this drug are needed and no consensus are published yet. The incidence of
195 osteosarcoma after teriparatide treatment is not negligible. For Watanabe et al., 9
196 males rats and 2 females rats developed osteosarcoma after 2 years of treatment
197 (total population of the study consisted of 55 rats) [15,19].

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

206 and wound differentiation [16].
207 Description of wound healing of the mandible after MRONJ with IV or oral ARDs
208 application has been already published and a systematic review was conducted but
209 with no history of a complete bone healing [17]. In 2015, Wehrhan et al., found that
210 the bone remodelling is related to Msx1 and DL-5 genes expression [18]. Msx1
211 stimulates osteoblast proliferation [18]. BPs inhibits Msx-1 expression [18]. When
212 BPs are stopped for more than their half-life, the expression of Msx-1 may increase,
213 and conduct to new bone formation [18]. The explanation of no more MRONJ is
214 elucidated but the new formation of the bone is not yet completely understood [17].
215 Stage III of MRONJ is a challenge for maxillofacial surgeon because of the high
216 morbidity of this disease. Conservative treatment (mouthwashes and antibiotherapy)
217 is the basis of MRONJ treatment but surgical treatment is often needed.
218 Sequestrectomy appears to be a good treatment and allows to avoid flap
219 reconstruction if mucosal healing is found under the sequester. Even if there is a lot
220 of publication about MRONJ, no consensus is reached yet, and more studies are
221 needed about new therapies. The take-home message in relation with MRONJ is the
222 importance of carry out oral examination before starting ARD treatment, and to
223 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

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- **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.

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All images were anonymized and no private data were provided allowing the patient's identification.

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Authors contribution:

Author	Contributor role
Maxime Debiève	Conceptualization, Investigation, Methodology, Data curation, Resources, Validation, Writing original draft preparation, Writing review and editing
Hervé Crevecoeur	Conceptualization, Investigation, Validation, Writing original draft preparation, Supervision, Writing review and editing

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