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ORIGINAL ARTICLE

Antiresorptive drug-related osteonecrosis of the jaws, literature review and 5 years of experience

S. Bernardi[1] · M. Di Girolamo[3] · S. Necozione[2] · M. A. Continenza[1] · T. Cutilli[3]

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Abstract

Purpose Bisphosphonate drug therapy provides benefits in the case of osteoporosis and carcinomas metastasizing to the bones, but it exposes patients to important side effects. The aim of this study was to investigate the incidence and the appropriate surgical treatment of bone lesions and fractures due to antiresorptive drug-related osteonecrosis of the jaws (ARONJ).

Methods Patients presenting with osteonecrosis lesions of the jaw, who were referred to the Maxillo-Facial unit of the University of L'Aquila, were considered for inclusion. Grade of the lesion and treatment choice was recorded for each patient. Descriptive statistics were calculated and the data were analysed with Chi-squared tests. A representative case of a fracture reduction with a supra-periostal approach is reported.

Results Among the 165 patients with ARONJ lesions, 112 were female and 53 were male. In total, 115 patients received intra-venous bisphosphonate therapy and 50 received oral bisphosphonate therapy. Five stage 2 lesions, three stage 2 lesions and two stage 3 lesions were not a consequence of dental procedures. Eighteen surgical bone excisions were performed and four pathological fractures were reduced. In one case (the reported one), the combined use of platelet-rich plasma and the supra-periostal approach leads to a successful 1-year follow-up.

Conclusions ARONJ lesions are a type of pathological bone disease affecting the jawbones. The pathology pathway remains a controversial and frequently discussed topic. A surgically conservative strategy seems to be the best way to assure a comfortable quality of life to those patients negatively affected by this condition.

Keywords Biphosphonates · Antiresorptive agent · Osteonecrosis of the jaw · Osteoporosis

Introduction

The use of bisphosphonate drugs has become more common during the last few years [1]. This drug therapy has been shown to provide numerous benefits in the case of osteoporosis and carcinomas metastasizing to the bones, but it exposes patients to several important side effects [2].

Numerous studies have shown an association between osteonecrosis in the jaws and treatment with bisphosphonates (ONJ), but few of these have analysed the conservative surgical therapy options [3]. It is commonly known that surgical interventions, such as surgical extractions or fracture reductions, dramatically increase the development of osteonecrosis in patients under bisphosphonate treatment [4]. This suggests that the less invasive and much more conservative surgical therapy option is the key to successful treatment of these patients [4].

Before performing a surgical treatment on a patient receiving bisphosphonate (BP) treatment, it is fundamental, when possible, to end the pharmacological treatment for a determined period. The last World Health Organization (WHO) guidelines suggest that treatment should be stopped at least 4–6 months before performing any surgical operation on the patient (operations that involve the bone). Obviously, the type of approach to the treatment changes depending on the type of drug intake [3]. BP drugs can be taken in two different ways,

✉ S. Bernardi
sara.bernardi@univaq.it

[1] Anatomy Division, Department of Life, Health and Environmental Sciences, University of L'Aquila, Via Vetoio, Coppito 2, 67100 L'Aquila, Italy

[2] Department of Life, Health and Environmental Sciences, University of L'Aquila, Via Giuseppe Petrini, Edificio Delta 6, Coppito, 67100 L'Aquila, Italy

[3] Maxillo-Facial Surgery Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, Via Lorenzo Natali 1: Località Coppito, 67100 L'Aquila, Italy

intravenously (iv) or orally (os). The side effects and the risks of surgical treatment differ greatly depending on the different actions of the drug administration route.

The definition of bisphosphonate-related osteonecrosis of the jaw (BRNOJ) has radically changed in the last year; the acronym has changed to antiresorptive-related osteonecrosis of the jaw (ARONJ). These changes have been well acknowledged at the 23rd European Association for Cranio Maxillo-Facial Surgery (EACMFS) Congress attended by Dr. Robert E. Marx, the first author to classify and describe osteonecrosis of the jaw and relate it to BP therapy. The aim of this manuscript is to report the frequency of the appearance of osteonecrosis lesions in patients receiving oral BP therapy, and to analyse the new therapy strategies before and during the surgical treatment, focusing on conservative surgical treatment methods. A representative case of fracture reduction with a supra-periostal approach is also reported.

Materials and methods

Patients referred to the Maxillo-Facial Unit of the University of L'Aquila-San Salvatore City Hospital, within the last 5 years (06/2011–06/2016). The inclusion criteria was to the presence of osteonecrosis lesions and receiving either oral or intravenous BP therapy. Exclusion criteria were: not being over 18 years old and the absence of consent to the participation to the study.

Appropriate surgical therapy was adopted, depending on the grade of the lesion and described in the results.

Statistical analysis

Descriptive statistics were calculated, including frequency distributions of the qualitative data. Further, Chi-squared and fisher exact tests were performed. Firstly, the tests were performed considering the association between the route of administration and the arising of the lesion without any previous dental intervention. In addition, the frequency of observed lesions was considered within the different stages of the lesions. The differences were considered statistically significant when $P < 0.05$. The statistical analyses were performed using SAS University Edition Software.

All patients gave informed consent for their participation to the study, and the study was approved by the ethical committee of the University of L'Aquila (N. Prot. 29575).

Results

Among the patients referred to the Maxillo-Facial Unit of the University of L'Aquila-San Salvatore City Hospital over the last 5 years, 165 patients presented with osteonecrosis lesions. Of these patients, 112 were female and 53 were male. Further, 70% were treated with zoledronic acid (iv) for oncologic reasons and 30% were treated with ibandronic acid (os) for osteoporosis (Table 1).

In terms of the lesions, 68 patients presented with stage 1 ONJ lesions, 74 patients presented with stage 2 ONJ lesions and 23 patients presented with stage 3 lesions. The stage 1 patients were treated with 0.12% chlorhexidine mouthwash for at least 3 weeks. Among this group, five patients presented with a spontaneous lesion.

The stage 2 patients were generally treated pharmacologically with the prescription of antibiotic therapy for 10 days. Among the stage 2 group, 22 received os BP therapy and 52 received iv BP therapy. Three of these 52 patients had a lesion raised spontaneously.

Of the 23 stage 3 patients, 22 were surgically treated. Of these, 18 stage 3 ARONJ lesions were excised and four pathological fractures were reduced, and so treated for 2 months. Among the stage 3 group, 21 received iv BP treatment and two received os BPs. Among the 21 oncological patients, four lesions arose after atraumatic loss of the permanent teeth, and thus were likely caused by chronic periodontitis (Table 2).

The Chi-squared test and Fisher exact tests comparing the route of administration and the spontaneity of the lesion were not statistically significant ($P > 0.05$).

The Chi-squared test and Fisher exact tests comparing the route of administration and the spontaneity of the lesion in the groups stage II and stage III were not statistically significant ($P > 0.05$).

These data are summarized in Tables 3, 4 and 5.

Surgical case

One of the pathological fractures was not an oncologic case, so a combination of the supra-periosteal approach and the use of platelet-rich plasma could be applied.

The patient, a 68-year-old female receiving treatment, was complaining of strong pain in the left inferior quadrant, and difficulty opening the mandible. The orthopantomograph revealed a pathological fracture in an alveolar site with two infected roots (Fig. 1).

The patient was put under general anaesthesia. The roots were extracted and the 1-cm bone necrosis was excised (Fig. 2). The fracture was then reduced using a titanium miniplate with a supra-periosteal approach. Platelet-rich plasma, obtained according to Di Staso et al. [5], was applied, and the site was sutured (Fig. 3).

Table 1 General data about the patients

Patients presenting ARONJ	Male	Female	BPs ev	BPs os
165	53	112	115	50

Table 2 Data regarding the stage of the lesion and the treatment performed

Stage	*N*	Route of administration	Type of treatment	Lesion araising
Stage I	68	OS	Chlorhexidine 0.12%	5 Spontaneous
Stage II	52	IV	Amoxicillin + clavulanic acid 3 gr × 10 days and metronidazole 2 gr × 10 days	3 Spontaneous
Stage II	22	OS	Amoxicillin + clavulanic acid 3 gr × 10 days and metronidazole 2 gr × 10 days	All due to dental procedures
Stage III	21	IV	Surgery (20)	4 Spontaneous–chronic periodontitis
Stage III	2	OS	Surgery	All due to dental procedures

Table 3 Contingency table comparing the different routes of administration with the frequency of lesions raised spontaneously

Route of administration	Lesion araised spontaneously			Chi-squared test	Fisher test
	No	Yes	Total		
IV	66	7	73	Not significant	Not significant
OS	87	5	92		
Total	153	12	165		

Table 4 Contingency table, Chi-squared test and fisher exact test significance comparing the different routes of administration with the frequency of lesions raised spontaneously within the stage II group

Route of administration	Lesion araised spontaneously			Chi-squared test	Fisher test
	No	Yes	Total		
IV	49	3	52	Not significant	Not significant
OS	22	0	22		
Total	71	3	74		

Table 5 Contingency table, Chi-squared test and Fisher exact test significance comparing the different routes of administration with the frequency of lesions raised spontaneously within the stage III group

Route of administration	Lesion araised spontaneously			Chi-squared test	Fisher test
	No	Yes	Total		
IV	17	4	21	Not significant	Not significant
OS	2	0	2		
Total	19	4	23		

The 8-month radiological follow-up showed healing of the fracture line (Fig. 4). The 12-month clinical follow-up showed significant healing of the oral mucosa (Fig. 5).

Discussion

The jawbone presents a unique bio-morphology in the human skeletal system. The jawbones are joined to the teeth, are covered by a relatively thin mucosa and are exposed to the microorganisms colonizing the oral cavity [6–8]. They are part of the phonatory and digestive apparatus and contribute significantly to the physiognomic function of the face. Even though the vascularization of the jawbone is rich, the vessels have a terminal course [9–11], and this feature makes it fragile to traumatic and inflammatory injuries.

The pathological basis of general bone tissue disorders (e.g., Paget's disease, osteogenesis imperfect, osteoporosis, bone metastases secondary to cancer) involves imbalance between the bone apposition of the osteoblasts and the remodelling performed by the osteoclasts. Currently, the treatment of bone disorders comprises the use of antiresorptive drugs such as hormone replacement therapy, selective oestrogen receptor modulators, BPs and denosumab. These therapies have been shown to improve clinical pain symptomatology and the incidence of pathological fractures [12]. However, their side effects primarily affect the jawbone, with the occurrence of osteonecrosis lesions, which often, but not always, arise subsequent to dental procedures.

Over the years, many models have been proposed to explain the mechanisms behind the presentation of these lesions, but the pathogenesis is not yet fully understood. To our knowledge, osteonecrosis lesions are caused by the inhibition of bone remodelling and the excessive inhibition of osteoclast activity by antiresorptive agents, the increased predisposition to oral bacterial infection due to BP administration, the suppression of remodelling due to the action of BPs and the migration of oral epithelial cells, the negative effects of antiresorptive agents on the immune system and the antiangiogenic effects of BPs [1, 3, 13–15].

In addition, the reason that osteonecrosis occurs only in the jawbone and not in other bone segments is not clear. Though, it has been found that BPs induce significant pathological changes in the cellular structures of the metaphysis. In particular, it was found that zoledronic acid causes a delay

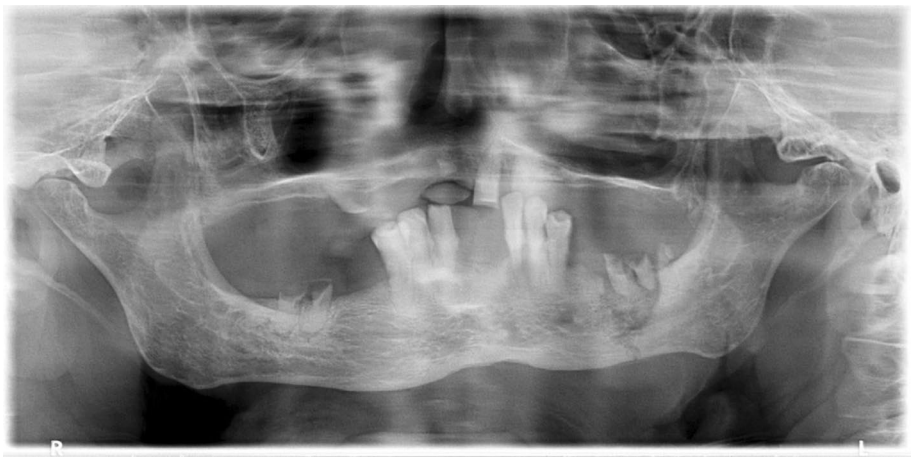

Fig. 1 Preoperative orthopantomograph

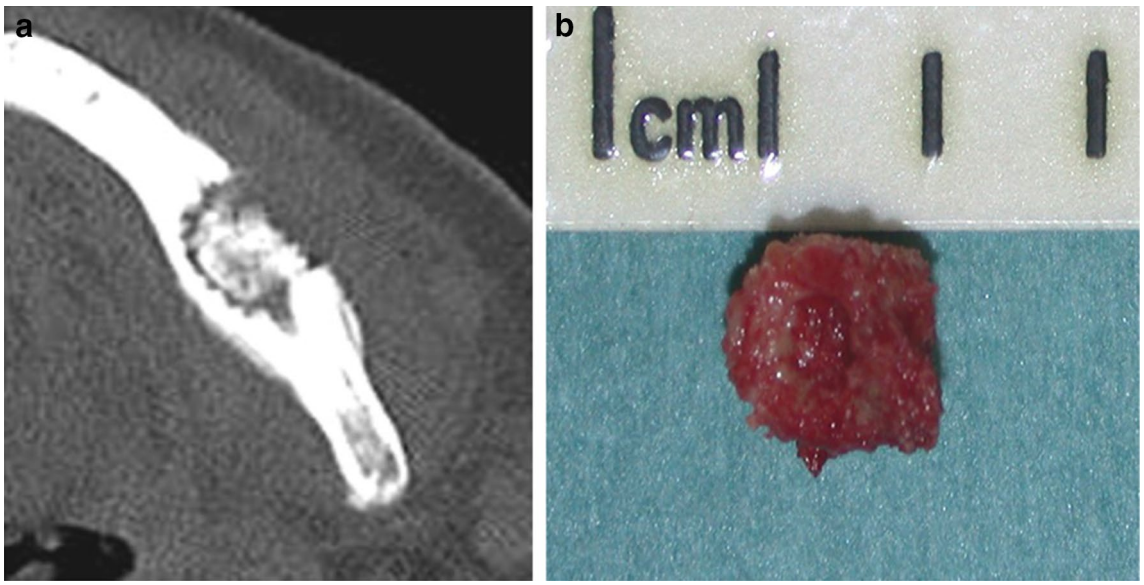

Fig. 2 **a** Computed tomography detail. **b** Lesion excised

in the removal of the cartilaginous matrix, which negatively affects bone development [16].

The reported incidence of ARONJs is variable, ranging from 0.7 to 12%, and the lesion appears to occur more frequently in women [1, 14, 17], as was also found in this study. Clinically, it is fundamental to identify this type of patient and to correctly diagnose the eventual bone lesion. The most recent accepted staging system proposed by the American Association of Oral and Maxillo-Facial Surgeons (AAOMS) [18] includes four different classes of patients, and the associated treatment management:

Stage 0 No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms.
Stage 1 Exposed necrotic bone, asymptomatic and with no evidence of infection.
Stage 2 Exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of exposed bone, with or without purulent drainage.
Stage 3 Exposed and necrotic bone in patients with pain, infection and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, resulting in pathologic fracture; extraoral fistula; oral antral/oral nasal communication; and osteolysis extending to the inferior border of the mandible or the sinus floor.

Stage 0 is of particular interest for the dentist. In this stage, all the preventive actions must be considered, including the avoidance of surgical extractions or wounds caused by an incorrect prosthesis, and the lowering of the microbiological load of the oral cavity. Stage 0 requires the clinician

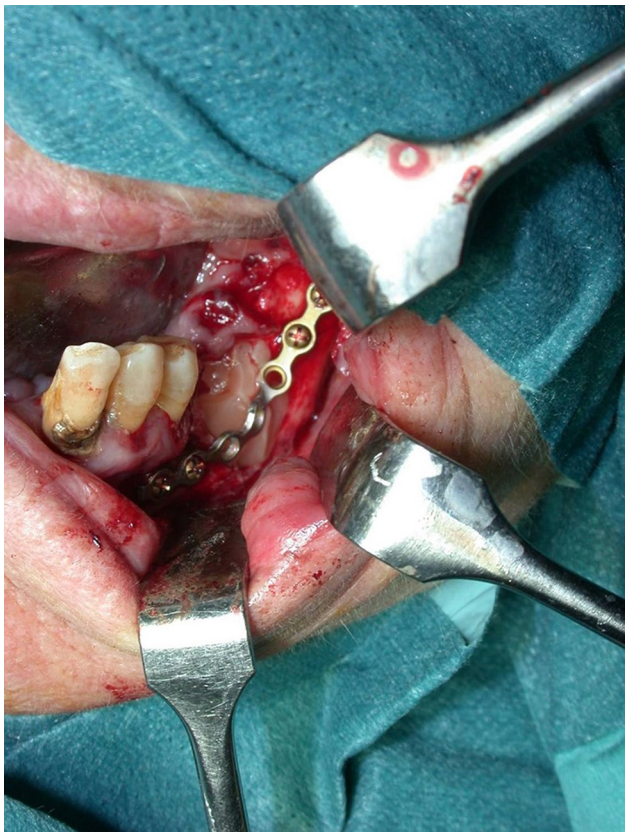

Fig. 3 Application of platelet-rich plasma and supra-periosteal fixation by means of titanium mini-plates

to pay particular attention to the condition of the patient, and to place the patient on a continuous control program.

Since the treatment of the bone necrosis is not standardized and even with surgical removal, the necrotic lesion can persist, the aim of the treatment should address the comfort of the patient. Consequently, secondary infections and pain have to be controlled.

When surgery is mandatory (such as pathological fractures), the strategy to minimally expose the bone margin and the periosteal tissues seems to be successful for restoring an acceptable quality of life in these type of patients. The supra-periosteal approach reported in the case presented is inspired by this strategy [18]. In addition, the application of platelet-rich plasma in the site allowed successful healing of the mucosa of the site, one of the first aims of the treatment of ARONJ lesions.

The regenerative properties of platelet-rich plasma are widely known [19, 20], and platelet-rich plasma is widely used as a precious aid in orthopaedic and bone surgeries, as well as on skin and deep dermatologic wounds [5]. The successful healing obtained in this case suggests that a combination of platelet-rich plasma with low-level laser therapy [21], and eventually with natural antioxidant molecules [22], could be used in the future for the treatment and management of bone osteonecrosis in non-oncologic patients.

In conclusion, we affirm that ARONJ lesions negatively affect the quality of life of patients, especially oncologic patients. Painful lesions affecting the oral cavity negatively influence feeding and the diet. The delivery of BP and antiresorptive agents should be accurate, and the patient should be fully informed of the possible side effects that can arise. Therefore, it appears that cooperation between the different medical specialists is crucial in order to fully assist and possibly prevent osteonecrosis lesions from arising.

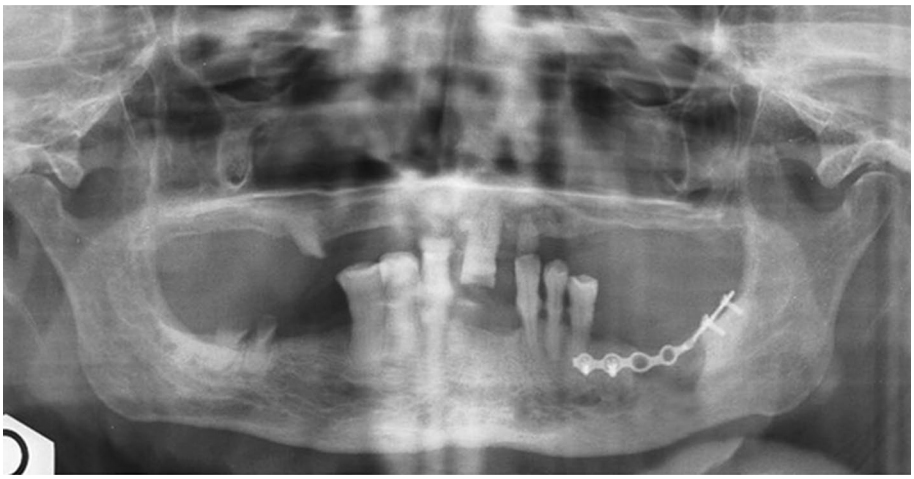

Fig. 4 Orthopantomographs at 8-month follow-up

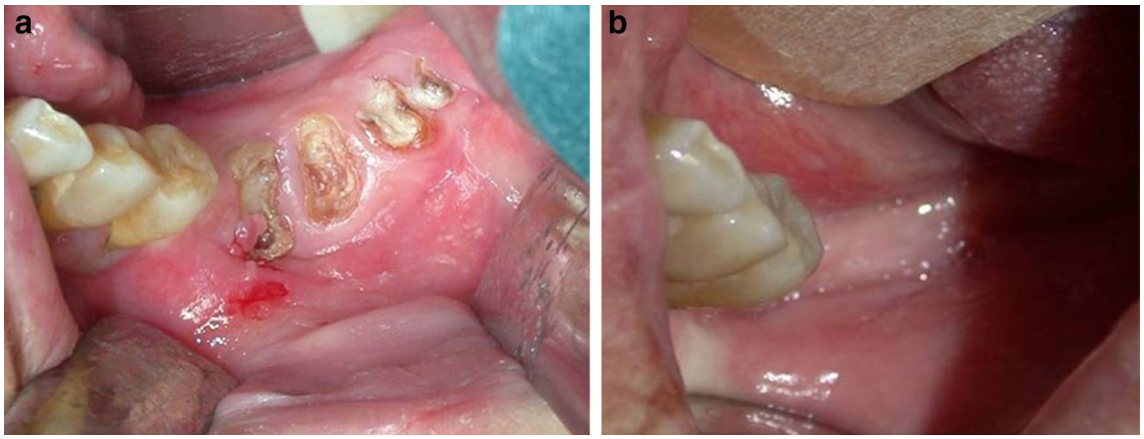

Fig. 5 **a** Clinical preoperative situation. **b** Clinical 12-month follow-up

Author's contribution Sara Bernardi and Tommaso Cutilli contributed to study conception and design; Mattia Di Girolamo contributed to data acquisition and writing of article; Stefano Necozione provided statistical analysis and review; and Maria Adelaide Continenza Sara Bernardi and Tommaso Cutilli contributed to editing, reviewing and final approval of article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Consent for the publication of the case report and any additional related information was obtained from the patients involved in this study.

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