Surgical Management of Medication-Related Osteonecrosis of the Jaw Patients Related to Dental Implants

Marco Nisi, DDS,* Rossana Izzetti, DDS, PhD,* Stefano Gennai, DDS, PhD,* Pierantonio Bellini, MD, OMFS,1 Filippo Graziani, DDS, PhD,* and Mario Gabriele, MD, DDS

Objectives: The aim of the present study is to report a case series of patients with peri-implant medication-related osteonecrosis of the jaw (MRONJ), in particular describing the onset of the condition and surgical treatment outcome.

Material and Methods: Fifteen consecutive patients with clinical diagnosis of peri-implant MRONJ were retrospectively included in the study. The sample was stratified on the basis of oral, pharmacological, and general health variables. The number of affected implants was recorded in all patients, and MRONJ staging applied. Surgical treatment was performed with a standardized operative protocol, involving implant removal, sequestrectomy, debridement of soft tissue, and bone curettage. Follow-up evaluating surgical outcome was performed at twelve months after surgery.

Results: In our study sample, patients were almost equally distributed in terms of underlying diseases in osteoporotic and oncologic patients. All MRONJ lesions were symptomatic, and in 6 patients bone exposure was detected. 40 implants in total were evaluated, with MRONJ being present around 29 implants. 12 patients were diagnosed with Stage III MRONJ, and 3 patients with Stage II MRONJ. Surgical treatment leads to complete healing in 86.7% of cases, with 100% success for maxillary MRONJ.

Conclusions: Surgical treatment seems to have a positive impact on MRONJ treatment also in cases of peri-implant involvement. However, monitoring and prevention are fundamental in patients under pharmacological treatment with anti-resorptive/antiangiogenic drugs, as peri-implant MRONJ can develop also in absence of specific traumatic events.

Key Words: Dental implants, medical related osteonecrosis of the jaw

Medication-related osteonecrosis of the jaw (MRONJ) is defined as a pathologic condition affecting the maxillary bones associated to the treatment with anti-resorptive/antiangiogenic drugs for the modulation of bone remodeling.1 Several disorders contribute to dysregulation in bone activity, including benign conditions (osteopenia, osteoporosis, and Paget disease) and malignant diseases (multiple myeloma and bone metastases). Different therapeutic protocols, including per os or intravenous administration of anti-resorptive/antiangiogenic drugs, may thus be applied.2

Among the adverse effects of antiresorptive drugs, Marx et al3 and Ruggiero et al4 initially described osteonecrosis of the jaws associated to the administration of bisphosphonate (BP) therapy, which was therefore defined as bisphosphonate-related osteonecrosis of the jaw (BRONJ).1,3 However, the increasing number of osteonecrosis cases related to the administration of other antiresorptive and antiangiogenic drugs lead to a change in the definition to MRONJ in 2014 by the American Association of Oral and Maxillofacial Surgeons.5

Medication-related osteonecrosis of the jaw is currently defined by the clinical presence of exposed bone or intraoral/extraoral fistula present for more than 8 weeks, history of administration of antiresorptive or antiangiogenic agents, and exclusion of previous head and neck radiation therapy or jaw metastases of other tumors.

The etiology of MRONJ is still unknown, while pathogenesis can be related to the fact that BPs and antiresorptive agents repress osteoclast-mediated remodeling of bone through disruption of intracellular pathways and inhibit angiogenesis.5 In the 2014 AAOMS position paper, risk factors for MRONJ were categorized as drug-related, demographic, local, and systemic or genetic factors.1

Oral surgical procedures, including tooth extractions, implant positioning, and periodontal surgery, in association with poor oral hygiene, periodontal infections, abscesses, and mobile dental prostheses, have been recognized as risk factors concurring to the development of MRONJ. Advanced age, smoking, corticosteroid therapy, and coexisting pathologic conditions are considered systemic factors favoring the development of MRONJ.5,6

While in literature it is reported the association of tooth extractions and MRONJ development, data is controversial on the relationship with implant placement. Two main facts seem to relate MRONJ to implants, the first regarding the risk of osteonecrosis associated to implant placement, and the second evaluating the presence of the implants themselves as a risk factor for necrosis development. A recent review by Giovannacci et al7 reports an
association between the presence of implants at the development of MRONJ. A potential role of patient general health condition and duration of antiresorptive treatment has been claimed to influence MRONJ development.7

Although some studies describe peri-implant MRONJ, currently there is a lack of studies directly addressing the issue of surgical treatment of this condition.2

The main aim of the present study was to describe the clinical and radiographic characteristics of 15 cases of peri-implant MRONJ. Its secondary objective was to evaluate the effectiveness of surgical treatment of peri-implant MRONJ, describing our results in terms of surgical outcome.

MATERIALS AND METHODS

Design of the Study and Sample

A sample of consecutive patients referring to the Unit of Dentistry and Oral Surgery, University Hospital of Pisa (Pisa, Italy) between January 2013 and December 2018 was retrospectively enrolled in this study. All the patients were surgically treated for this condition.

The study was conducted according to the criteria set by the Declaration of Helsinki. Ethical committee approval regarding the performance of the present retrospective study was obtained through an exemption related to retrospective data collection.

Inclusion criteria were history of administration of antiresorptive/antiangiogenic drugs and clinical diagnosis of peri-implant MRONJ. The sample was stratified depending on systemic factors and pharmacologic and local variables.

Systemic factors were considered:
- Comorbidities: smoking habit, diabetes, hypertension, rheumatoid arthritis
- Underlying diseases requiring administration of antiresorptive/antiangiogenic drugs: osteoporosis, metastatic breast cancer, multiple myeloma, metastatic prostate cancer

Pharmacologic variables were related to the drug administered, both in terms of type of medication (zoledronate, alendronate, ibandronate, neridronate, and denosumab) and of therapeutic protocol (length of therapy and cumulative dose).

The diagnosis of MRONJ was made by an experienced examiner (MN) on the basis of clinical and radiographic examination (panoramic radiograph and computed tomography (CT)). In case of uncertainty, an expert operator was consulted (MG).

Clinical evaluation allowed to determine local variables describing MRONJ characteristics, such as localization, presence of bone exposure, suppuration, neurological symptoms (pain/paresthesia), extra-oral fistulisation, and oro-antral communication.

Radiographic examination allowed determining the extension of MRONJ and the possible presence of bone sequestrum. (Figs. 1 and 2)

Design of the Study and Sample

After the diagnosis of peri-implant MRONJ, all patients were medically treated with a session of professional oral hygiene, together with reinforcement of domestic oral hygiene and prescription of 2% chlorhexidine mouthwash to be used twice daily for 14 days. Patients were also given amoxicillin with clavulanic acid (2 g/day for 14 days) plus metronidazole (750 mg/day), and were evaluated clinically two weeks later.

After medical treatment, resolution of the infection and pain relief were obtained, while signs of complete healing were not observed. Surgical approach was then performed. Pharmacological treatment included a standardized administration protocol of antibiotics, with the following scheme: 3 g of amoxicillin administrated preoperatively and 2 g/day for two-weeks following surgery. In cases of allergy to penicillin, oral azithromycin (1 g/day) was administrated.

All surgical interventions were performed under local anesthesia by a single expert operator specialized in oral surgery. Surgical treatment included removal of dental implants involved, sequestrectomy, debridement of soft tissue, and curettage of bone. Residual sequestra were removed to ensure healing by primary intention. At the end of the surgical intervention, the closure of the surgical site was assured by suturing without mobilization of the flap with a resorbable/non resorbable 5–0 suture thread; the removal of visible
surgical procedure. (A) Preoperative view of peri-implant MRONJ, occlusal view: suppuration and inflammation are present around dental implants. (B) Preoperative view of peri-implant MRONJ, lateral view: bony defect around implants can be observed, with loss of keratinized gingiva and partial exposure of the fixture and of mandibular bone. (C) After flap elevation, MRONJ can be observed. (D) Mandibular bone after implant removal. (E) Wound closure with resorbable suture thread and soft tissue repositioning. (F) Removed implants and necrotic bone around the fixtures.

FIGURE 3. Surgical procedure. (A) Preoperative view of peri-implant MRONJ, occlusal view: suppuration and inflammation are present around dental implants. (B) Preoperative view of peri-implant MRONJ, lateral view: bony defect around implants can be observed, with loss of keratinized gingiva and partial exposure of the fixture and of mandibular bone. (C) After flap elevation, MRONJ can be observed. (D) Mandibular bone after implant removal. (E) Wound closure with resorbable suture thread and soft tissue repositioning. (F) Removed implants and necrotic bone around the fixtures.

RESULTS

Sample Characteristics

Fifteen patients, 13 women and 2 men with a mean age of 71.8 ± 8.7 years (range 52–79 years), were included in the study over a 5-year period. General sample characteristics are shown in Supplemental Digital Content, Table 1, http://links.lww.com/SCS/B191. In almost 50% of cases, administration of antiresorptive/antiangiogenetic drugs was related to the treatment of osteoporosis. Among osteoporotic patients, the majority of the sample (6 subjects) was treated with alendronic acid (70 mg/week; cumulative dose: 18,060 mg) and neridronic acid (10 mg/month: cumulative dose: 3360 mg) and zoledronic acid (4 mg/month; cumulative dose: 71.8 mg). Among oncologic patients, 6 subjects were treated with antiresorptive/antiangiogenetic drugs was related to the treatment of osteoporosis and zoledronic acid in oncologic patients, with mandible being more affected than the maxilla. Although spontaneous healing of MRONJ lesions has been seldom reported in literature,10,11 medical treatment with antimicrobial agents and surgery may be required depending on ONJ stage. As reported on the AAOMS position paper, stages I and II benefit from conservative management, while stage III requires surgical debridement/resection to obtain longer term palliation of infection and pain. However, if stage II is refractory to conservative management, surgical debridement of the affected bone is recommended to reduce soft tissue irritation. Our results showed good performance of surgical treatment, with a high percentage of MRONJ resolution. MRONJ surgical treatment outcome has been reported in literature to be stage-dependent.1 Consistently with previous literature and AAOMS guidelines, complete healing was observed in all Stage II MRONJ, while in 2 Stage III patients resolution was not achieved.

As reported by Oteri et al12 the management of ONJ patients includes not only the general treatment of MRONJ in terms of pain relief and prevention of the development of new areas of necrosis, but also the preservation of patients’ quality of life (QoL). Therefore, in these patients the resolution of acute infection and pain provides a support to the management of MRONJ, leading to a significant improvement of perceived QoL.

Current guidelines regarding the possible association between MRONJ and implant positioning raise the issue of the impossibility to establish a direct link due to a lack of data. Recently, it has been claimed that implant placement, being a surgical procedure, is as risky as tooth extraction. However, the presence of an implant itself seems to be a risk factor for ONJ development.

Several case series report the percentage of MRONJ developed around implants, either shortly after positioning or without apparent causal relationship (Supplemental Digital Content, Table 6, http://links.lww.com/SCS/B191). Goss et al report an effective risk of implant failure associated to therapy with oral BPs, occurring both when positioning implants in 7 patients) were not affected. Non-affected implants were almost equally distributed in the mandible (6 implants) and in the maxilla (5 implants). In 2 patients, MRONJ was present both around implants and in another non-implant related site.

The mean number of affected implants in the mandible was slightly higher than in the maxilla (2.1 and 1.6 respectively), although not statistically significant.

Surgical Outcome

At 12-month follow-up, complete healing was obtained in 86.7% of cases, with 100% success for maxillary MRONJ. Two cases affecting mandible were resistant to surgical therapy (Supplemental Digital Content, Table 5, http://links.lww.com/SCS/B191). Stratification indicated 100% disease resolution for all stage II lesions, 83.3% disease resolution for stage III (10 subjects).

Histology

Histological analysis showed the presence of necrotic bone tissue characterized by the presence empty osteocytic lacunae and empty Haversian systems and Volkmann canals. Necrotic area was surrounded by an infiltrate of neutrophils and plasma cells. In the peripheral area was detected the presence of actinomycetes.

DISCUSSION

The present study reports the experience of our group in the diagnosis and surgical treatment of peri-implant MRONJ. In our study sample, MRONJ was more frequently developed in patients under pharmacological treatment with alendronic acid for osteoporosis and zoledronic acid in oncologic patients, with mandible being more affected than the maxilla. Although spontaneous healing of MRONJ lesions has been seldom reported in literature,10,11 medical treatment with antimicrobial agents and surgery may be required depending on ONJ stage. As reported on the AAOMS position paper, stages I and II benefit from conservative management, while stage III requires surgical debridement/resection to obtain longer term palliation of infection and pain. However, if stage II is refractory to conservative management, surgical debridement of the affected bone is recommended to reduce soft tissue irritation. Our results showed good performance of surgical treatment, with a high percentage of MRONJ resolution. MRONJ surgical treatment outcome has been reported in literature to be stage-dependent.1 Consistently with previous literature and AAOMS guidelines, complete healing was observed in all Stage II MRONJ, while in 2 Stage III patients resolution was not achieved.

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patients under pharmacological treatment with BPs and in patients starting therapy with BPs with previously integrated implants. In particular, the issue of patients developing osteoporosis requiring pharmacological treatment, with possible loss of implant integration, is raised.13

Lazarovici et al15 consider BRONJ development a late complication of implant therapy showing no direct relationship to surgery. In this sense, it is advisable to perform long-term follow-up, and in cases of BRONJ development to prescribe antibiotic therapy with doxycycline 100 to 200 mg/d. Surgical treatment with implant removal is reserved to antibiotic resistant symptoms.15 In our study sample, surgery was performed after medical treatment with combined antibiotics and professional oral hygiene. Moreover, surgical treatment involved bone debridement and sequestrectomy in addition to implant removal.

Jacobsen et al highlighted a predominance of BRONJ localization in the posterior region of the jaws, suggesting posterior implant localization as a risk factor for BRONJ development, and describe a histological pattern corresponding to inflammation and Actinomyces infection.16

López-Cedrún et al recorded the presence of coexisting pathologic conditions and health-threatening habits, but due to limited study sample firm conclusions could not be drawn.17 In our study, we stratified patients depending on comorbidities and underlying diseases, but did not find correlation with the onset of MRONJ due to limited study sample. Further studies on larger populations are therefore needed to better assess the role of coexistent pathologic conditions.

Kwon et al18 report an average time of implant-related BRONJ onset of 13 to 27 months after the beginning of BP therapy, with the minority of patients considered as "implant surgery-triggered" BRONJ cases. Moreover, it is described the histologic aspect of implant-related BRONJ lesions.18 In our sample, medium onset of MRONJ was 67.7±36.1 months after treatment beginning. As previous described by Marx and collaborators histologic analyses show the presence of necrotic bone tissue characterized surrounded by an infiltrate of neutrophils and plasma cells. In the peripheral area was detected the presence of actinomycetes.14

Giovannacci et al suggest that increased risk of developing MRONJ may be related to antiresorptive drugs on bone remodeling. In fact, bone around implants is subject to continuous modification, in particular when considering implants loaded with prostheses. The inhibition deriving from antiresorptive therapy thus may lead to MRONJ development also in patients with osteointegrated implants.7

Troeltzsch et al17 highlight the possible role of peri-implantitis as a risk factor for MRONJ development around dental implants, being observed more frequently in patients with long treatment of antiresorptive/antiangiogenic drug treatment. The improvement of oral hygiene could play an important role in preventing MRONJ onset in general and avoid the development of peri-implantitis around dental implants, which seems to be a trigger factor for peri-implant MRONJ.17

In our sample, MRONJ development was evaluated in patients administered BPs and in 1 patient treated with Denosumab. A previous case series by Pogrel and Ruggiero20 reported late implant failure in patients treated with BPs or Denosumab, with bone exposure around implants and development of a sequestrum.

The characteristics of our sample confirm the findings of other authors, with the mandible being more affected than the maxilla and an association with the administration of zoledronic and alendronic acid.21

According to previous literature, MRONJ development around implants was not related to apparent triggering factors. In a recent meta-analysis by Stavropoulos et al, it is stated that peri-implant MRONJ is not fully understood as a pathologic condition, hypothesizing as concurring factor the reduction of bone remodeling and subsequent vulnerability to infection.

Attempts have been made to stratify the risk of ONJ development in patients undergoing pharmacological treatment with anti-resorptive drugs. In a study by Peisker et al,22 the potential role of serological bone turnover markers was investigated to evaluate whether their variation could determine a higher risk of ONJ development after oral surgical procedures. Although patients affected by MRONJ showed decreased values of serum bone alkaline phosphatase (s-BAP), results did not reach statistical significance. However, a potential role of serological biomarkers may be helpful in evaluating the risk of MRONJ development in at-risk patients.

Considering surgical treatment, to the best of our knowledge we are the first to report surgical outcome of Stage II/III peri-implant MRONJ.

Relying on the experience deriving from previous studies on MRONJ not involving dental implants, we applied a standardized surgical protocol for the treatment of peri-implant MRONJ, obtaining positive outcome in almost 90% of cases. In a work by Graziani et al,23 resective surgery showed to be an effective approach to the treatment of Stage II/III due to limited morbidity, while the outcome of conservative surgery seemed less predictable. In our sample, surgical approach involving implant removal and bone debridement with sequestrectomy proved to be effective, by providing complete healing in 86.7%, in agreement with other studies reporting the clinical outcome of MRONJ surgery.

In particular, complete healing was observed in all Stage II patients, while in Stage III surgical treatment was successful in 83.5% of cases. High success rate in patients with stage III ONJ suggests that the presence of MRONJ limited to the peri-implant area may potentially be a positive prognostic factor for surgical treatment.

Our study is the second in literature to evaluate surgical outcome in peri-implant MRONJ, although showing some differences with the work of Lazarovici et al.15 In fact, while in their study surgical treatment was reserved to antibiotic-resistant MRONJ, we performed surgery in all patients after initial medical treatment. However, the main limitation of our study is the retrospective design. Further prospective studies are therefore needed to better assess the impact of anti-erosive/antiangiogenic drugs on dental implants and their relationship with MRONJ development. Nonetheless, our results suggest a beneficial role of surgery in treating peri-implant MRONJ and highlight the importance of monitoring and prevention in patients under pharmacological treatment with anti-resorptive/antiangiogenic drugs, in which peri-implant MRONJ can develop also in absence of specific traumatic events.

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