



Case report

aPDT associated with sequestrectomy in the treatment of osteonecrosis in cancer patients with metastasis: Case report

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ARTICLE INFO

Keywords:

Bisphosphonate-associated osteonecrosis of the jaw
BRONJ
Surgery
Oral
Photodynamic therapy
Lasers
Case report

ABSTRACT

Introduction and importance: Bisphosphonates are drugs that have demonstrated effectiveness in the prevention and treatment of bone metastases from malignant neoplasms and other diseases of bone metabolism and although they represent a risk factor for osteonecrosis.

Presentation of case: The present case depicts a patient with prostate neoplasia and metastases, referred to the dental department because he presented severe periodontal infection in the previous incisors of the mandible and was under treatment by intravenous zoledronic acid. A panoramic x-ray showed a marked bone loss with a periodontal infection that indicated the tooth exodontia of the affected teeth. However, 2 months after the removal of the dental elements, bone sequestration was detected a CT scan confirmed that. Surgery was then performed to remove mandibular bone sequestration and photodynamic therapy (aPDT) treatment for decontamination of the affected area.

Discussion: There was a tissue reconstitution of the site in 3 weeks and total eradication of bone necrosis with aPDT treatment associated with bone sequestration.

Conclusion: aPDT has proven to be an effective complementary treatment for the process of tissue decontamination and photostimulation in cases of BRONJ.

1. Introduction

Zoledronic acid belongs to a group of medicines called bisphosphonates. This drug has an amine grouping that potentiates the action of the drug, leading to the suppression of bone regeneration with antiangiogenic properties and activator of T lymphocytes, which culminates in neoplastic reduction [1]. These drugs are deposited in the bone matrix and are released gradually during prolonged periods, with a half-life of approximately 10 years, which due to this cumulative condition increases the risks of the development of osteonecrosis [1]. There is a pathophysiological change in blood nutrition, which may lead to tooth loss, infections, or lesions in the bone. The mandible is the site most affected by osteonecrosis, associated with a higher concentration of this drug in the maxillary bones due to the greater blood supply, in addition to accelerated bone turnover. The extractions are the main local factor associated with the development of this disease [1,2].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has defined a pattern for the characterization of osteonecrosis associated with bisphosphonates: bone tissue exposed in the maxillary facial region that persists for more than eight weeks in patients undergoing current or previous treatment with bisphosphonate and who do not present a history of head and neck radiotherapy [2]. Currently, other medications like the anti-resorptive drugs, denosumab show high attraction by hydroxyapatite and their ability to incorporate bone as key points in their relationship with osteonecrosis. In the case of denosumab, a monoclonal antibody, it acts on osteoclast precursors and does not make bone incorporation, therefore its half-life, time of use, and the possibility of suspension should be considered when planning an invasive dental procedure [3].

In the present article, photobiomodulation with aPDT is shown in osteonecrosis cases caused by zoledronic treatment.

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<https://doi.org/10.1016/j.ijscr.2022.107487>

Received 7 June 2022; Received in revised form 1 August 2022; Accepted 7 August 2022

Available online 10 August 2022

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2. Case report

Male patient, F.A.C., 69 years old, with primary neoplasm in the kidney and metastasis in different organs, was referred to the dental department of the Cancer Hospital of Ribeiro Preto, Brazil, for evaluation of periodontal infection in the region of the lower incisors (Fig. 1a). The case was related in accord with SCARE Guidelines [4]. In the anamnesis patient reported the use of the drug zoledronic acid, a year ago, to control bone metastases. The suspension of zoledronic acid and extraction of the four lower incisors was realized. The patient showed after 2 months an area of bone exposure with the presence of necrosis and purulent secretion (Fig. 1b). Diagnosis of osteonecrosis by bisphosphonate (BRONJ) (Fig. 1c), classified as stage 2 with evolution to 3, according to AACOM [3].

In 2021, the MASCC (Multinational Association of Supportive Care in Cancer) and ISOO (International Society of Oral Oncology) (9) compiled scientific evidence and published recommendations for clinical management and treatments strategies for osteonecrosis and according to such conducts, local irrigation with chlorhexidine 0.12 % and prescription of metronidazole 250 mg was performed every eight hours for seven days, infection control; in addition, the patient received instructions for mouthwash at home four times a day with 0.12 % chlorhexidine and was instructed on the diet so that there was no type of trauma at the site. However, there was an increase in the lesion and a complaint of increased pain sensitivity in the following 4 weeks. Due to the undesirable condition, the oncologist suspended the use of zoledronic acid again for 1 month to perform the surgical procedure for the removal of bone-mandibular necrosis.

Surgical management was performed, which consisted of local debridement and sequestrectomy with a low-rotation surgical motor per

minute coupled with the cylindrical carbide surgical drill, followed by abundant irrigation with saline solution with the detachment of muco-periosteal tissue and total removal of contaminated tissue (Fig. 1d).

Then, the tissue was collected with formaldehyde at 3.7 % for pathological examination (Fig. 2a–d). Photodynamic therapy (aPDT) was performed on the surgical site using low-intensity laser equipment. In this case, 0.005 % Chimilux (DMC group - São Carlos - Brazil) methylene blue was used as a photosensitizer, for 5 min in the region. In combination with laser irradiation Therapy EC (DMC group - São Carlos - Brazil) at red wavelength 660 nm. The application protocol laser, used the power of 100 mW, the application time of 90 s, with 9 J of energy, and fluency of 320 J / cm² for point, radiating at three points (Fig. 3a). Finally, the tissue suture for bone coating was carefully performed (Fig. 3b). The patient had stable hemodynamic values during all phases of treatment.

In the postoperative phase, the patient was treated with more than 2 times aPDT, and showed adequate healing, with normal texture and color. Currently, the patient is stable and rehabilitated with a prosthesis (Fig. 2c).

3. Discussion

Bisphosphonates are drugs that have demonstrated effectiveness in the prevention and treatment of bone metastases from malignant neoplasms and other diseases of bone metabolism and although they represent a risk factor for osteonecrosis, their suspension may lead to the progression of the patient's disease. In addition, the cumulative effects of bone incorporation of the drug should be considered, its route of administration, in this case, intravenous, and that zoledronic acid, a bisphosphonate considered the third generation, is 10,000 times more potent than a first-generation bisphosphonate, therefore, even used for 1 year, as in the present case, the average dose of the drug deposited in bone is possibly more representative than of a bisphosphonate of lower potency [5]. We saw in this case report in the histological analysis of the bone matrix with the absence of osteocytes cells that maintain the metabolism of the tissue. This analysis confirms the tissue necrosis and the difficulty in the repartitioning process of the remnant (Fig. 2b–d). Such observations should score the therapeutic clinical decision of the multidisciplinary team. Determining the appropriate time for intervention and suspension or alteration of the drug used, seeking an appropriate window of opportunity for the procedure, when it is mandatory and conservative therapy does not achieve the expected success.

The literature describes that not all cases in which bone sequestration is performed in treatments with bisphosphonates present favorable results. For this reason, the association of a photobiomodulation effect with PDT along with its antibacterial action may favor this type of treatment as described in the protocol of the clinical case presented [5].

It appears that the therapy conducted in the association of the surgical maneuver with aPDT was successful. aPDT consists of the interaction of light with the photosensitizer and oxygen, generating free radicals that induce severe damage to microbial cells, leading to their death [6]. This therapy is associated with surgical maneuvers effectively eradicating stage 2 osteonecrosis in the mandibular region. Osteonecrosis in this case occurred after surgical intervention of exodontia, which is to the findings of a retrospective study by Vescovi et al. [5]. Relative healing and improvement of the clinical picture were also highlighted by Bodem et al. [7] who opted for a surgical approach in patients with stage 2 and 3 osteonecrosis, using intravenous zoledronate [5].

It should be noted that other known and validated procedures can also be performed in the treatment of osteonecrosis depending on its stage. In severe cases where cancer persists, oncologic treatment must be prioritized, and the preservation of quality of life, along with pain control, infection, and necrotic areas must be continuously followed up with oncologic treatment [1].

In the present case, during follow-up consultations of 3, 4, and 6 months, full coverage of the bone area exposed by gingival mucosa was

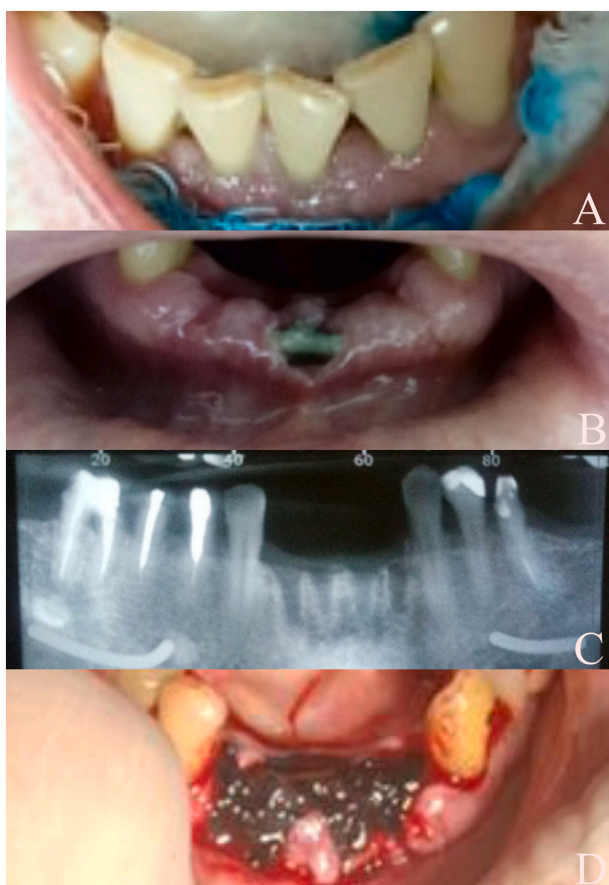


Fig. 1. a) periodontal infection in the region of the lower incisors. b) necrosis and purulent secretion. c) jaw radiography. d) necrosis and purulent secretion.

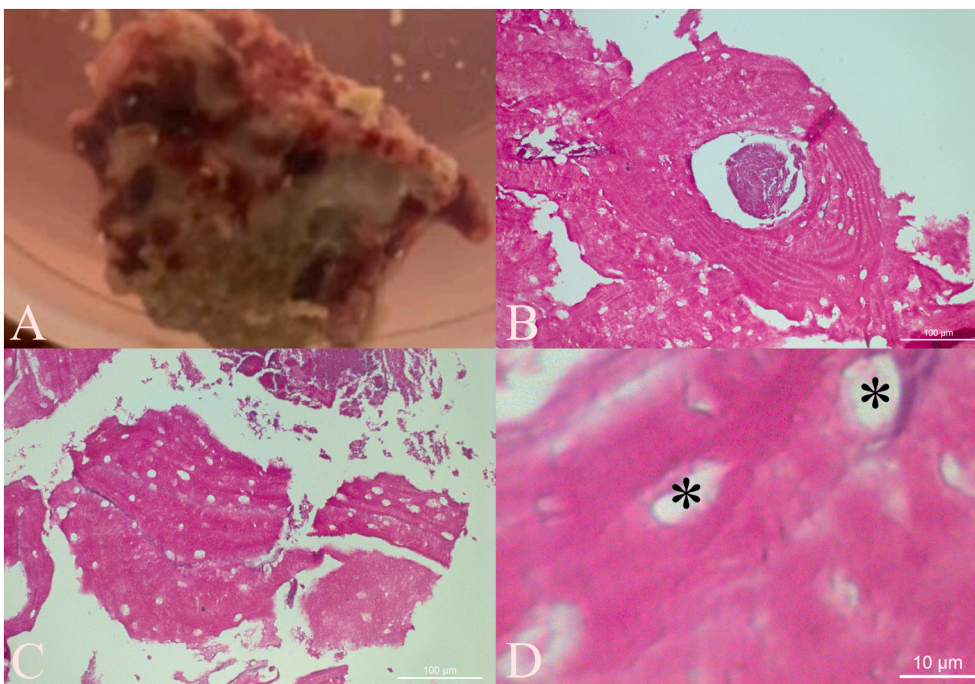


Fig. 2. a) Necrosis tissue collected. b–d) Histopathological analysis showed necrosis with bone acellular (H&E). * Osteocyte absent.



Fig. 3. a) aPDT protocol 660 nm laser with methylene blue. b) tissue suture and hemostasis. c) final image with prosthetic rehabilitation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

observed. Applied, noninvasive laser therapy was well tolerated by the patient. It does not cause adverse effects and promotes induction of tissue repair, pain control and modulation of the inflammatory process [6], in this case, aPDT combined with surgical therapy, promotes microbial reduction that seems to have contributed greatly to clinical success and is revealed as a promising adjuvant therapy.

4. Conclusion

It is of paramount importance to recommend a multidisciplinary team to every patient who starts bisphosphonate therapy, as a preventive measure to mitigate bisphosphonate osteonecrosis. The PDT technique as a complement to the surgical procedure is shown to be effective in combating osteonecrosis caused by biphosphonates.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

This case report didn't require review by Ethics committee, Cancer Hospital of Ribeirão Preto, São Paulo, Brazil.

Funding

The authors declare that they had no financial support for the development of this research.

Guarantor

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Research registration number

Not applicable.

CRediT authorship contribution statement

Juliano Abreu Pacheco: Conceptualization, Participated in the surgery, data collection, case analysis, and writing of the manuscript.

Beatriz Tholt: writing of the manuscript

Eugênia Velludo Veiga: Supervision and validated the case data.

Hermes Pretel: Conceptualization, supervision and writing of the manuscript.

Declaration of competing interest

The authors declare no any conflict of interest in this paper.

Acknowledgements

We thank the Hospital do Câncer de Ribeirão Preto for their work with the community, the NUPEN Institute for their support, and the histology technician Pedro Sérgio Simões for his partnership and histological processing.

References

- [1] R.G. Coropciuc, K. Grisar, T. Aerden, M. Schol, J. Schoenaers, C. Politis, Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases: conservative treatment is effective up to stage 2, *Br. J. Oral Maxillofac. Surg.* 55 (8) (2017) 787–792, <https://doi.org/10.1016/j.bjoms.2017.06.014>.
- [2] American Association of Oral and Maxillofacial Surgeons <collab>Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws, *J. Oral Maxillofac Surg.* 65 (3) (2007 Mar) 369–376, <https://doi.org/10.1016/j.joms.2006.11.003>.
- [3] N. Yarom, C.L. Shapiro, D.E. Peterson, C.H. Van Poznak, K. Bohlke, S.L. Ruggiero, C. A. Migliorati, A. Khan, A. Morrison, H. Anderson, B.A. Murphy, Medication-related jaw osteonecrosis: MASCC/ISOO/ASCO clinical practice guideline, *J. Clin. Oncol.* 37 (25) (2019 Sep 1) 2270–2290, <https://doi.org/10.1200/JCO.19.01186>.
- [4] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) Guidelines, *Int. J. Surg.* 84 (2020) 226–230.
- [5] P. Vescovi, G. Campisi, V. Fusco, G. Mergoni, M. Manfredi, E. Merigo, L. Solazzo, M. Gabriele, G.M. Gaeta, G. Favia, F. Peluso, Surgery-triggered and non-surgery-triggered bisphosphonate-related osteonecrosis of the jaws (BRONJ): a retrospective analysis of 567 cases in an Italian multicenter study, *Oral Oncol.* 47 (3) (2011 Mar 1) 191–194, <https://doi.org/10.1016/j.oraloncology.2010.11.007>.
- [6] R.Y. Tateno, L.F. Palma, W.R. Sendyk, L. Campos, Laser and antimicrobial photodynamic therapy for the management of delayed healing following multiple dental extractions in a post-radiotherapy patient, *Photodiagn. Photodyn. Ther.* 30 (2020 Jun), 101764, <https://doi.org/10.1016/j.pdpdt.2020.101764>.
- [7] J.P. Bodem, C. Schaal, S. Kargus, D. Saure, C. Mertens, M. Engel, J. Hoffmann, C. Freudsperger, Surgical management of bisphosphonate-related osteonecrosis of the jaw stages II and III, *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* 121 (4) (2016 Apr 1) 367–372, <https://doi.org/10.1016/j.oooo.2015.10.033>.