

Multiple systemic diseases complicated by bisphosphonate osteonecrosis: a case report

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Summary

Aims: this work aims at demonstrating that multiple systemic conditions, in association with the development of bisphosphonate associated osteonecrosis of the jaw (ONJ), increase the risk of complications and may lead to hospitalization. For this reason the dental approach to patients with multisystem disease should be carefully managed by a team of specialists.

Case report: a case of mandibular necrosis associated with intake of oral bisphosphonates in a complex systemic context is described. **Results and discussion:** many different diseases and systemic conditions may draw the line at oral surgery. Multiple treatments (e.g. antithrombotic, calcium channel blockers, diuretics, antibiotics and bisphosphonates) can alter the normal physiological response to tissue healing.

Conclusions: patients taking bisphosphonates for more than three years (i.e. the term over which the risk of ONJ increases according to the literature, in presence of complex systemic situations, need to be carefully managed during the pre-operative, peri-operative and post-operative phases through a synergistic collaboration among different kind of specialists.

Keywords: bisphosphonate osteonecrosis, oral surgery, therapeutic approach, CTX.

Introduction

Bisphosphonates, orally or parenterally administered, represent a class of drugs that affect the bone metabo-

lism, interfering not only with the biological activity of the osteoclasts, but also with the normal endothelial turnover at the level of oral tissues (3,4).

For this reason, bisphosphonates may delay the healing of surgical wounds in patients undergoing oral surgery (5). According to some authors (6), bisphosphonates, parenterally administered to patients suffering from cancer associated with bone metastasis, may have an additional or synergistic antitumour effect with standard anticancer agents *in vitro* aimed at blocking the tumour invasion (6). Notwithstanding, these drugs may produce serious complications, which can cause the development of osteonecrosis of the jaw (ONJ) after oral surgery. Bisphosphonate ONJ, first described by Marx and Stern in 2002 (7), is a disease occurring in the jaws and originating from the maxillary alveolar bone, which may subsequently extend to baseline bone or branch.

Bisphosphonates, targeted at the osteoclasts, produce a strong inhibition of the metabolism.

The biological action of bisphosphonates leads to a reduced formation of bone multicellular units, which are formed by small islands of osteoclasts, osteoblasts and adjacent blood vessels (8).

Bisphosphonates inhibit the osteoclast action, thus blocking the complete resorption of the damaged bone. Patients treated with bisphosphonates may undergo three types of surgical wounds healing: normal healing, delayed healing and ONJ (9).

Healing is considered normal when the epithelialization of surgical wounds is complete within a month; it is considered delayed when it lasts one to three months with or without surgical re-intervention.

Instead, ONJ presents a bone exposure that lasts for more than three months in patients taking bisphosphonates and following a surgical procedure.

The treatment goals for oral ONJ are different from intravenous ONJ because it is more curable. The first goal in treatment is initial intermediate-term palliation followed by either spontaneous resolution or resolution gained by debridement surgery. The initial therapy for oral ONJ is prevention of pain with the use of 0,12% chlorhexidine 30ml swish-and-spit regimen three times daily. If pain or infection is present, the antibiotic regimens are indicated. Marx et al.(10) have found that 40% of oral ONJ cases resolve in 6 month period without debridement. The remaining 60% of cases show clinical and radiographic signs of improvement, such as loosening or separation of the necrotic bone from adjacent healthy bone or a radiographic involucrum separating a sequestrum from adjacent bone. At that time, local office-based sequestration/débridement with a primary closure can resolve ONJ.

Although intravenous ONJ is mostly permanent, most

cases can be prevented or managed if they develop with only few cases requiring resection for resolution (10).

Case report

In May 2009 Mrs G.L. came to our attention at the dental clinic of S. Gerard in Monza. The patient was 83 years old and complained about discomfort in the area of the symphysis, where, four years earlier two implants for a ball attachment overdenture had been placed. The clinical examination showed a symptomatic localized suppurative lesion in the intraforaminal portion, adjacent to the implants. The lesion was very advanced, creating a cutaneous fistula with an extraoral vent in the chin (Fig. 1-2). At the radiographic examination (orthopantomography of the jaws), it could be observed a cottony-looking radiolucent lesion in the intraforaminal portion, associated with bone sequestrations (Fig. 3).

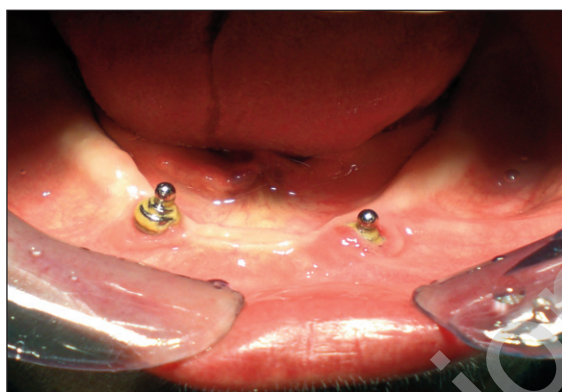


Figure 1. Initial clinical situation.



Figure 2. Extraoral fistula.

The clinical and radiographic examination diagnosed a third grade ONJ, according to Ruggiero's classification (11), linked to consumption of oral bisphosphonates.

A meticulous remote and recent pathological anamnesis revealed important multiple systemic complications. The condition of osteoporosis suffered by the patient and diagnosed for over 20 years had led to the fracture of the femoral neck, following a fall; hence, an intervention of hip

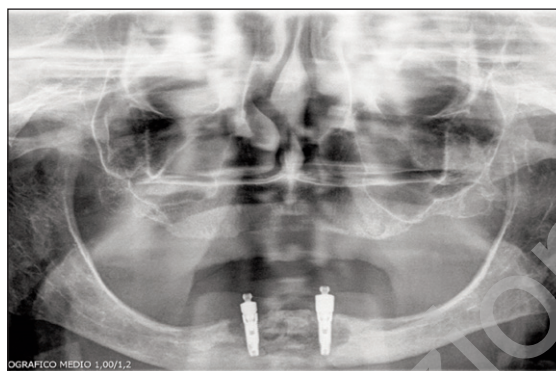


Figure 3. Initial Orthopantomography.

replacement was carried out in 2003. Osteoporosis is also a cause of consumption of systemic alendronate 70 mg/die orally, that was suspended one month before the visit to S. Gerard's hospital.

The anamnesis also revealed a condition of liver cirrhosis, diagnosed in 1999, resulting in a time series of multisystem disorders, including a major renal failure.

The patient was treated daily with omeprazole (10 mg daily), furosemide (500mg/die), potassium (100 mg/die), Budesonide (400 mg/die), Vitamin D (880 IU), Allopurinole (300mg/die).

Because of the complex systemic condition of the patient and the serious osteonecrosis at the time of the visit, a detailed radiographic analysis was performed by TC Dentascan and the value of serum telopeptide (hereafter CTX) was assessed.

The CTX is a serum test used in the preoperative evaluation of the risk of delayed healing in patients taking bisphosphonates after invasive procedures. The serum value in the patient was 0.115 ng/ml. The values of CTX can be grouped into three categories from high to medium and low risk of ONJ. Marx (12, 13) suggested that CTX values lower than 0.100 ng/ml are associated to high risk of ONJ, values ranging from 0.100 ng/ml to 0.150 ng/ml to moderate risk and values higher than 0.150 ng/ml to low risk.

Cross sections of TC Dentascan clearly showed that the necrotic lesion preserved both the buccal and lingual cortical (Figs. 4, 5).

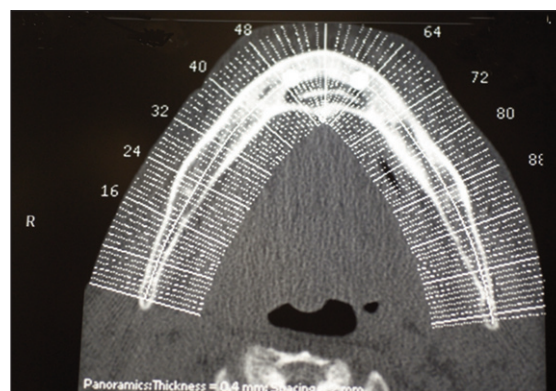


Figure 4. Initial Dentascan Tc.

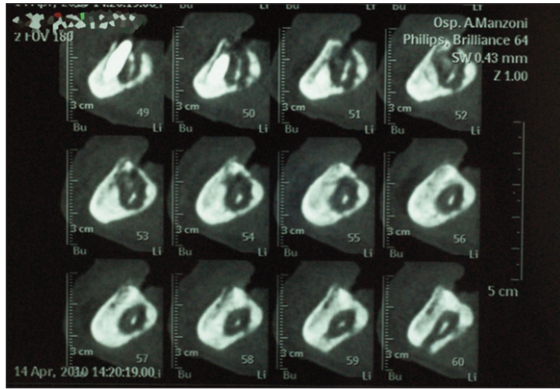


Figure 5. Initial Dentascan Tc, cross sections.

A stereolithography model obtained by tomography (Fig. 6-7) facilitated the planning of surgery: despite the surgical procedure could increase the risk of emimandibulectomy, the removal of the two implants appeared essential to decrease the disease processes responsible of osteonecrosis.



Figures 6, 7. Stereolithography model.

Two weeks before surgery the patient had antibiotic prophylaxis consisting of amoxicillin and clavulanic acid in tablets of 1 g every 12 hours and metronidazole in tablets of 250 mg every 8 hours, omeprazole in tablets of 20 mg once daily for the duration of the antibiotic therapy, associated with applications of chlorhexidine gel 0.5%. In the operating room the implants were removed under

general anaesthesia with piezoelectric surgery, allowing a precise and micrometric conservative cutting (14) (Fig. 8) and a bone curettage was performed without holding the emimandibulectomy maintaining a thin state of cortical vestibular that assures the muscle insertion.

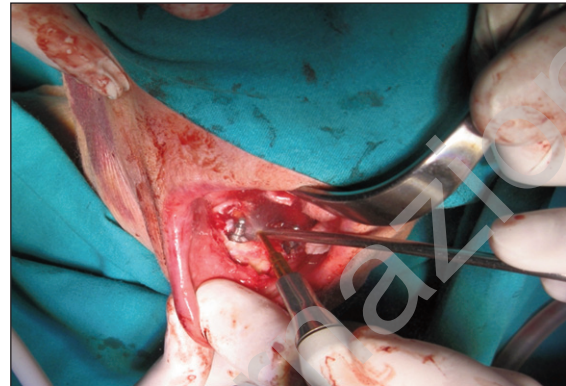


Figure 8. Implants removal with piezoelectric surgery.

The surgery was concluded placing a silk suture 3/0 with separate stitches, maintained for about 10 days, in order to facilitate the juxtaposition of the flaps, thus ensuring a first intention healing (Fig. 9).

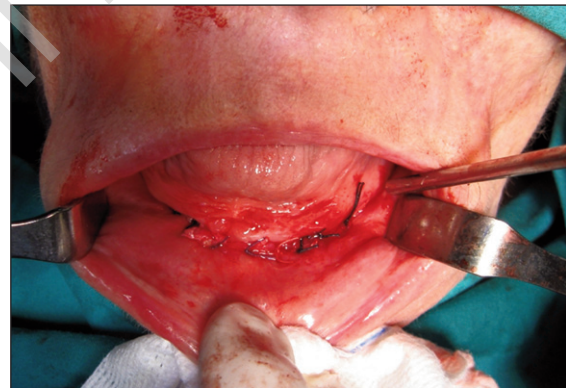


Figure 9. Suture 3/0.

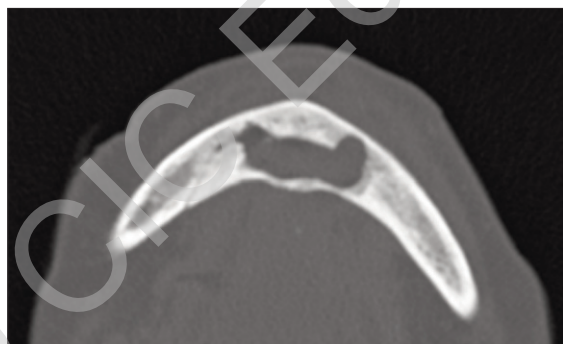
Six hours after surgery, the patient had serious bleeding complications, leading to a significant edema of the mouth floor, which caused the closure of the upper airway. It was therefore necessary to perform an emergency operation to resolve the bleeding complications.

The patient was maintained for two days in medically induced coma in intensive care to prevent complications and was kept under observation for 15 days, before discharging. The same antibiotic prophylaxis was extended for the week following surgery in order to avert infection of the wound.

The patient was reassessed about six months after surgery to check the healing of the hard and soft tissues of the oral cavity (Fig. 10). Post-operative Tc was performed for 20 days after surgery (Fig. 11-12). The clinical examination showed that the oral tissues responded adequately with normal healing.



Figure 10. Wound healing 6 months later.



Figures 11,12. Post-operative Tc 20 days later.

A soft and fresh diet for the days following surgery was recommended to the patient, because it is impossible to replace the previous prosthesis and to avoid overloading on the operated mandibular portion when the residual cortical bone is very small.

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS) (15), it is considered good practice to stop bisphosphonates before surgery, follow-

ing a specific protocol. In particular, if the intake of bisphosphonates lasts for more than three years it is necessary to stop bisphosphonates at least three months before surgery, delaying the resumption until three months after surgery.

In case of urgent oral surgery, it is considered good practice to submit patients to the appropriate procedure rather than maintain the condition of pain and infection.

Overall, three months after stopping bisphosphonates, the precursors of osteoclasts recovered their activity, allowing a good bone healing.

It is anyway crucial to remove any source of acute infection in the oral cavity to prevent the risk of ONJ in this situation.

Discussion

This case study shows that the serious systemic situations of the patient contributed to develop severe post-operative bleeding complications, with the need of a further surgical intervention.

The cause of post-operative bleeding was associated with coagulopathy leading to cirrhosis and thus altered prothrombin and thrombin times.

The high risk of post-operative complications in patients with systemic complicated conditions makes it necessary to manage them in hospitals in order to operate quickly in case of complications.

An accurate and careful follow-up is also recommended in order to monitor the patient to prevent possible recurrence.

This case report demonstrates that patients treated with oral bisphosphonates in the presence of systemic and complicated pictures characterized by ONJ can heal properly through a quick and appropriate pharmacological therapy and surgery.

Conclusions

Systemic conditions of patients with important medical histories, generally older than 60 years, affected by osteoporosis and treated with oral bisphosphonates can be often multiple and complicated.

Although several authors and Marx in 2005 (16) claim that patients with osteoporosis have an estimated risk of developing osteonecrosis ranging between 0.01% and 0.04%, or a low risk of developing this complication, in rare cases of onset of osteonecrosis this complication presents severe clinical characteristics. The reason may be related not only to the oral bisphosphonates intake, but also to the basic systemic diseases that compromise the body response to surgical trauma and to potential infections (13).

It is clear that patients characterized by multiple systemic histories complicated by ONJ associated with the recruitment of bisphosphonates need integrated and specialized medical assistance and that can be guaranteed only by only a hospitals.

This is particularly important because of the high risk of post-operative complications, in case there is need and urgency to perform invasive surgery related to oral therapy for ONJ.

It is therefore possible to conclude that patients characterized by complicated systemic conditions and diagnosed with ONJ must be included in a therapeutic procedure that ensures a rapid and careful solution of possible complications related to treatments to which they are submitted through the consultation and collaboration of the different branches of medical specialists.

These patients should be included in follow-up programs to monitor the status of achieved and maintained health of oral tissues over time.

Bisphosphonates have a prolonged half-life and are characterized by the elimination of their portion, that is the short side chain R1 participating in the bond with the mineralized bone matrix, occurring in the long term. The half-life of alendronate is approximately 12 years (2).

In addition, according to Marx (6), alendronate is the most potent bisphosphonate taken orally in terms of power and half-life; therefore, among oral bisphosphonates alendronate is the one producing the highest risk of developing ONJ.

It is worth noting that among oral bisphosphonates it is also necessary to consider the type of drug taken. In patients with multiple systemic conditions this consideration is even more important to prevent severe complications.

Ethics

The authors declare that the presented study was carried out in accordance with the ethical standards established in the Declaration of Helsinki.

The authors state that they have no conflict of interest. The authors state that they have not received institutional funds for this study.

The authors declare that the informed consent was obtained from all participants before their enrolment in the study.

Patient consent

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References

1. Sussman G. The impact of medicines on wound healing. *Pharmacist* Nov. 2007;26(11):874-878.
2. Sook - Bin W, Hellstein W J, Kalmar R J. Systematic Review: Bisphosphonates and Osteonecrosis of the Jaws. *Ann Intern Med* 2006;144:753-761.
3. Gonzalez-Moles MA, Bagan-Sebastian JV. Alendronate-related oral mucosa ulcerations. *J Oral Pathol Med* 2000; 29:514-518.
4. Demerjian N, Bolla G, Spreux A. Severe oral ulcerations induced by alendronate. *Clin Rheumatol.* 1999;18:349-350.
5. Magremanne M, Vervaet C, Dufrasne L, Duclerq I, Legrand W, Daelmans Ph. Bisphosphonates et ostéo(chimio)nécrose maxillo-mandibulaire. *Rev. Stomatol. Chir. Maxillofac* 2006;107:423-428.
6. Statz TA, Guthmiller JM, Humbert LA, Johnson GK. Intravenous Bisphosphonate – Associated Osteonecrosis of the Jaw. *Journal of Periodontology* 2007;78 (11): 2203-2208.
7. Marx RE, Stern DS. Biopsy principles and techniques. *Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment.* Chicago, Quintessence, 2002, p 36-38.
8. Corrado A, Cantatore FP. The bisphosphonates: chemical characteristics, skeletal biological effects and extra-skeletal effects. *Reumatismo* 2005;57(3):142-153.
9. Allen MR, Kubek DR, Burr DR, Ruggiero SL, Chu TM. Compromised osseous healing of dental extraction sites in zoledronic acid-treated dogs. *Osteoporosis International* 2010;11: 1433-2965.
10. Marx Re, Sawatari Y. Bisphosphonates and bisphosphonate induced osteonecrosis. *Oral Maxillofacial Surg Clin N Am* 2007;19:487-498.
11. Ruggiero S, Gralow J, Marx RE, Hoff AO. Practical Guidelines for the prevention, diagnosis and treatment of osteonecrosis of the jaws in patients with cancer. *Journal of Oncology Practice* 2005;1(2):7-13.
12. Marx R E, Cillo JE, Ulloa JJ. Oral Bisphosphonate induced osteonecrosis: Risk Factors, prediction of risk using serum CTX testing, prevention and treatment. *J Oral Maxillofac Surg* 2007;65(12): 2397-2410.
13. Marx Re, DDS. Reconstruction of Defects caused by Biphosphonate-Induced Osteonecrosis of the jaws. *J Oral Maxillof Surg* 2009;67(Suppl 1):107-119.
14. Vercellotti T. Technological characteristics and clinical indications of piezoelectric bone surgery. *Minerva Stomatologica* 2004;53 (5):207-214.
15. AAOMS (American Association of Oral and Maxillofacial Surgeons). Position Paper on Bisphosphonate Related Osteonecrosis of the Jaws. *J Oral Maxillofac Surg* 2007;65:369-376.
16. Marx RE, Sawatari Y, Fortin M et Al. Biphosphonate induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg* 2005;63:1567-1575.