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Post biphosphonate mandible osteonecrosis: A case study and literature review

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Abstract

Purpose: Bisphosphonates have proven effective in reducing pain and skeletal events in bone metastases treatment. However, there is a long-term complication called osteonecrosis of the jaw, which has been reported for more than a decade. Despite various professional recommendations, there is no international consensus on the best therapeutic strategy. Prevention is crucial, and a multidisciplinary approach must be tailored to each stage of the condition.

Design: We present a case of osteonecrosis of the jaw in a patient with metastatic breast cancer who was receiving 4 mg injectable zoledronic acid.

Result: The patient stopped treatment with zoledronic acid and received systemic treatment (analgesics, antibiotics), with the resolution of symptoms.

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Authors contributions

Bambara H Aboubacar and Zerbo Nina Assanatou 2 jumelle contributed to the study conception and design. Data acquisition: Bambara H Aboubacar. Quality control of data and alogorithms: Zerbo Nina Assanatou 2 jumelle and Ki Thierry Romuald. Data analysis and interpretation: Bambara H Aboubacar and Valerie Odero-Marah. Statistical analysis: Bambara H Aboubacar and Zerbo Nina Assanatou 2 jumelle. Manuscript preparation: Bambara H Aboubacar and Oué draogo Y C Laetitia. Manuscript editing: Bambara H Aboubacar and Zerbo Nina Assanatou 2 jumelle.Manuscript review: Valerie Odero-Marah. Valerie-Odero-Marah also contributed in part of the funding support for the submission of this manuscript. All authors reviewed the final manuscript.

Consent to participate

The individual included in this study provided written informed consent.

Declaration of competing interest

None declared.

Conclusion: ONJ is a serious condition associated with taking BP that can impact oral health and quality of life. Our study highlights the effectiveness of systematic treatment in managing ONJ with BP-related alterations. Preventative measures, such as regular dental consultations, play a vital role in reducing the risk of ONJ. Multidisciplinary management is essential to addressing the different stages of the condition.

Keywords

Osteonecrosis; Mandible; Bisphosphonates; Breast cancer

1. Introduction

Osteonecrosis of the jaw (ONJ) is a condition where necrotic bones become exposed in the oral cavity of patients who have been treated with bisphosphonates, without a history of cervicofacial radiation and persists for more than 6–8 weeks without healing [1]. Bisphosphonates (BP) are osteoclastic inhibitors that are widely used in the prevention of bone metastases and the treatment of hypercalcemia in malignant diseases, as well as in benign bone diseases such as osteoporosis and Paget's disease [2]. However, they can also cause ONJ, with a prevalence ranging from 0 to 27.5% depending on the method of administration [2]. The risk of ONJ is higher in oncology patients, with an incidence of 1–15% [2]. The first cases of ONJ were described by Marx in 2003 [3], and the number of cases has been increasing [1]. In this report, we present a case of ONJ in a patient who was taking BP. We aim to highlight the clinical characteristics of ONJ and provide a review of the literature on prevention and management strategies.

Patient and observation

A 56-year-old female patient with no particular pathological history was treated in 2019 for Grade II mSBR Nonspecific Infiltrating Carcinoma of the right breast, triple negative, Ki 67 at 50%, classified cT3N1M0. She underwent Patey type surgery and 3 chemotherapy treatments according to the FAC60 protocol (5FU 600 mg/2, Doxorubicin 60 mg/m2, Cyclophosphamide 600 mg/2) and 3 Docetaxel treatment (100 mg/m2) without additional external radiation. In March 2021, the patient's cancer progressed loco-regionally and remotely (pulmonary and bone), and she started receiving weekly taxol and 4 mg zoledronic acid intravenously every 28 days without prior stomatological consultation. In August 2021, she was referred to the oncology and clinical hematology department of the University Hospital of Bogodogo in Ouagadougou, for further care. After her 5th session of zoledronic acid, the patient experienced severe pain of the left jaw, making it difficult for her to sleep. The pain was not relieved by anti-inflammatory analgesics and was rated at 5 according to the Visual Analog Scale (VAS). Upon examination, there was gingival edema, with an erythematous mucosa, shiny, warm to the touch and dental mobility (Fig. 1). The patient was sent for consultation with dentistry and after clinical examination, an orthopantomogram found a thickening of the desmodontal space with osteolysis, giving the bone a "wet sugar" appearance (Fig. 2).

The patient had dental treatment, including dental avulsion. However, six weeks later, there was progressive swelling of the jaw, and a scan of the maxilla revealed an osteolytic

deficiency of the body of the jaw or bone destruction in the jaw (Fig. 3). The diagnosis of ONJ was confirmed. The treatment with zoledronic acid was stopped, and the patient was given opioids and antibiotics, with progressive resolution of symptoms for about three weeks. A decrease in the volume of the jaw associated with the disappearance of the inflammatory syndrome and progressive reduction of the doses of opioids was noted.

2. Discussion

Bisphosphonates (BPs) have demonstrated their effectiveness in reducing pain and reducing the incidence of skeletal events in the treatment of cancer bone complications [4,5]. However, a long-term complication of BP treatment called osteonecrosis of the jaw (ONJ) has been reported for more than a decade. In addition, other treatments, in particular antiangiogenics, have also been implicated in the occurrence of ONJ [3,6]. The term MRONJ (medication related osteonecrosis of the jaw) was introduced in 2014 by the American Association of Oral and Maxillofacial Surgeons (AAOMS) and is graded in four stages [7]. There is currently consensus on the latter term when osteonecrosis is associated with pharmacological treatments [8].

2.1. Pathophysiology and risk factors

The mechanism of ONJ occurrence is not well understood, and several pathophysiological hypotheses have been suggested, including the inhibition of bone remodeling, angiogenesis, infectious factors, genetic factors, or the immune system [2,9]. There are multiple risk factors associated with ONJ. It is more common in malignant disease (100 times greater risk) and when intravenous BPs are used [1,2,10]. In oncology, the most important risk factors include the dose and duration of BP treatment, especially if it is greater than 2 years [2], followed by the type of BP. The highest risks are those containing a side-chain nitrogen such as zoledronate (9.5 times higher risk than pamidronate) and denosumab [1,2,11]. In our case, the patient began to present symptoms after the administration of the 5th course of zoledronic acid 4 mg. Other factors that can contribute to ONJ are described: drug (concomitant use of corticosteroids or anti-angio-genic agents), local [2,9] (poor oral condition or injury on dental prosthesis or inflammatory oral pathology) [2], site (greater incidence on the jaw (65–73%) compared to the maxilla) [2,12], the female gender, certain comorbidities (anemia, diabetes, smoking, cancer), and genetic factors [2,7]. In our patient's case, ONJ was located in the jaw which is common due to the significant bone remodeling due to the biomechanical constraints of the masticatory forces, the oral environment where the bone is quickly in direct contact with the oral flora in case of mucous membrane breach [13].

2.2. Clinical study

The symptoms of ONJ can initially be discreet and not very specific. These can include ill-defined pain, dental mobility not explained by the condition of the tooth, gingival edema, mucous erythema, or ulceration of the mouth's lining. These symptoms can appear spontaneously or in the course of surgical treatment. In more advanced stages, there may be altered sensitivity in the territory of the lower alveolar nerve or even a mandibular fracture can occur [14]. Imaging plays an important role in the diagnosis of ONJ. The choice of

exam depends on individual preference and availability of exams [14]. It's important to note that the radiographic presentation do not necessarily correlate with the clinical stages or the duration of exposure to BP [13,15–17]. The radiographic findings may include osteolysis/ostesclerosis, enlargement of the alveolar ligament, thickening of the lamina dura, periosteal affixing [13,18], bone sequestration, perforation, or signs of maxillary sinusitis [13]. In our patient's case, an orthopantomogram revealed thickening of the desmodontal space with osteolysis, giving the bone a "wet sugar" appearance. Histologically, studies have shown a dysfunction of bone resorption with the presence of giant, hypernucleated, inactive osteoclasts and necrotic bones. The osteocytic network is disrupted with enlarged spans and reduced spinal space [13,19].

2.3. Prevention

ONJ prevention is the most important measure when prescribing a BP or denosumab [2 20 21]. First, it requires the identification of patients at risk. This involves oral rehabilitation, the elimination of alcohol and tobacco consumption, the realization of an orthopantomogram and, if necessary, invasive dental care before the administration of a BP [3 12]. It is recommended to provide information to patients to maintain excellent oral hygiene during treatment with regular monitoring of the oral condition at least every 6 months. Unfortunately, our patient had not benefited from a dental consultation prior to the administration of zoledronic acid 4 mg. The AAOMS recommends discontinuing PBs three months before and three months after invasive dental surgery and until complete mucosal healing [27].

2.4. Treatment

Despite the numerous occupational recommendations [7,8,21–26], there is no international consensus on the best treatment approach for ONJ [27]. According to the AAOMS, the treatments' goals are to relieve pain, sterilize the infectious site, and limit the progression or onset of a new ONJ cases. AAOMS offers treatment by stage (Table 1) [7]. The treatment strategy is generally adapted to the stage of the disease, underlying pathology, general condition of the patient, and their preferences. Patient education and reduction of modifiable risk factors such as managing diabetes, quitting smoking, and reducing alcohol consumption are important considerations [14]. The decision to continue or discontinue the causative treatment should also be discussed. Two therapeutic approaches are commonly used [14]: conservative treatment and surgical treatment (Table 2). The literature generally supports initial conservative treatment, especially up to stage 2. Surgery may be considered in combination with medical treatment in case of failure of medical treatment alone or for stage 2 or 3 cases. However, the use of invasive surgical treatment remains a subject of controversy. In our case, treatment with zoledronic acid was discontinued and the patient was put on opioids and antibiotics, resulting in progressive resolution of symptoms after 3 weeks.

3. Conclusion

ONJ, an odontostomatological complication associated with bisphosphonates, is a serious and debilitating condition that greatly impacts patients' quality of life. It occurs through

various mechanisms, hence the importance of preventive measures including prior stomatological consultation that are a key factor in reducing risks. Effective management requires a multidisciplinary approach that must be adapted to the specific stages of the condition.

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Fig. 1.
Left jaw tumefaction of patient.

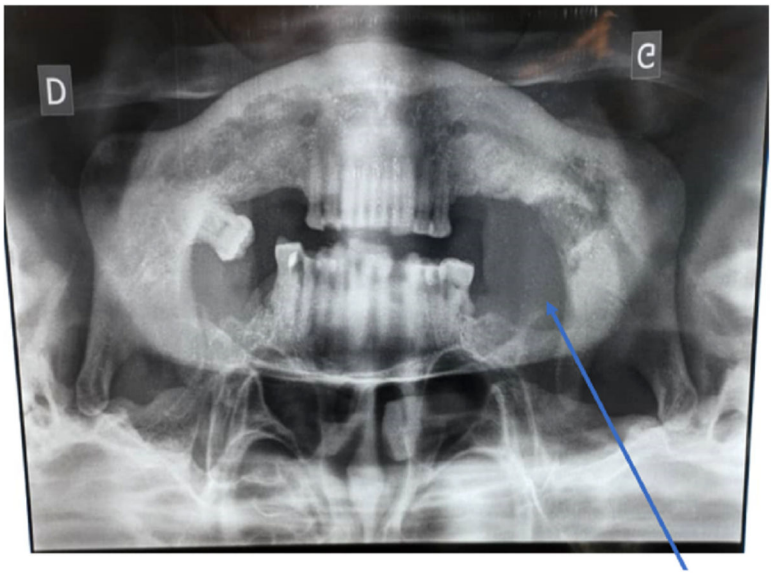

Fig. 2.
The orthopantomogram of a clinical examination showing osteolysis.

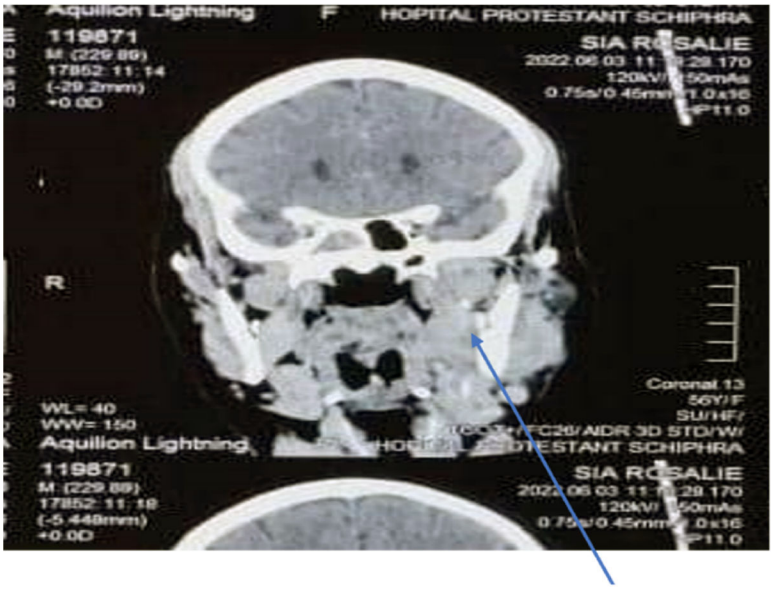

Fig. 3.
Osteolytic deficiency of the body of the jaw in scan of the maxilla.

Table 1

Treatment by stage (American association of oral and maxillofacial surgeons) [7].

Classification of osteonecrosis of the jaw	Therapeutic strategies
Patient at risk: **Patient exposed to bisphosphonates without evidence of necrotic bone**	No treatment; patient education
Stage 0: No clinical evidence of necrotic bone but presence of symptoms and specific clinical signs	analgesics, antibiotics
Stage 1: Asymptomatic lesions with bone exposure without infectious signs	Antiseptic mouthwashes; follow-up every 3 months; patient education; revision of indications for continuation of bisphosphonates
Stage 2: Exposed necrotic bone or bone fistula associated with signs of infection with or without purulent drainage	Oral antibiotics; antiseptic mouthwashes; analgesics; surgical debridement
Stage 3: Exposed bone, pain, inflammation, involvement of maxillary sinuses, cutaneous fistulas, pathological fractures	Antiseptic mouthwashes; antibiotics; painkillers; surgical debridement/resection to control infection and pain

Table 2

Treatment type for osteochondrosis [14].

Type of NMCO treatment	
Action on modifiable risk factors: smoking cessation, alcohol, balancing diabetes	
Conservative treatment	
Basic Conservative Measures	***Local treatment*** Brushing Manual cleaning by the practitioner Antiseptic mouthwashes and 3% hydrogen peroxide Resection of spicules or sequestrations
Conservative drug modalities “external”	***General treatment*** Painkiller Antibiotics Pentoxifyllin and tocopherol Teriparatide Laser Hyperbaric oxygen therapy Ozone application
Surgical treatment	
Conservative, under local anesthesia	Curettage Debridement Sequesterctomy Marginal resection
Invasive, under general anesthesia	Wide sequestration with cover flap Bone resection to bleeding margins Mandibulectomy switch (or maxillectomy) and reconstruction by: - local rags - Pediculated flaps - open flaps
Other therapeutic modalities	
Fluorescence-guided bone resection	
Autologous platelet concentrates	
Future: stem cells	