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Osteonecrosis of the jaw: An update

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Abstract

Introduction: Osteonecrosis of the jaw (ONJ) is a well-known pathological condition in oncology arising from bisphosphonate use. In recent years, the number of cases of drug-related osteonecrosis of the jaw has steadily increased due to the introduction of new immunological drugs.

Objective: To analyze the literature on osteonecrosis of the jaw and its relation to drugs.

Methodology: The search was performed in PubMed, SCOPUS and Google Scholar databases. The quality of the articles was assessed using PRISMA guidelines. The terms "osteonecrosis jaw", "etiology", "epidemiology", "diagnostic methods", "oral manifestations", "treatment", in conjunction with logical Boolean operators AND, OR and NOT were used.

Results: Although the pathogenesis of ONJ is still unclear, genetic factors have shown an important role in this disease. It is more frequent in patients who ingest bisphosphonates, whether orally or intravenously, with a frequency of 65% in the mandible. Necrotic bone exposure is one of the most frequent oral manifestations that occur. The most characteristic diagnostic methods include orthopantomography, magnetic resonance imaging and computed tomography. One of the treatments to consider is the education and instruction in oral hygiene that the patient should perform/take, as well as the use of oral antibacterial rinses.

Conclusion: Every patient treated with bisphosphonates is susceptible to present mandibular osteonecrosis when undergoing invasive dental procedures, therefore, it is necessary to consider which are the most significant clinical characteristics, as well as the diagnostic methods by which we can identify it in the patient; the treatments are very varied depending on the situation in which each case is found.

Keywords: osteonecrosis, bisphosphonates

1. Introduction

Osteonecrosis of the jaw (ONJ) is a well-known pathological condition in oncology arising from bisphosphonate (BP) use. In recent years, the number of cases of drug-related osteonecrosis of the jaw (MRONJ) has steadily increased due to the introduction of new immunological and molecular target drugs for cancer treatment [1].

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse drug reaction consisting of progressive bone destruction in the maxillofacial region of patients [2]. It is a chronic osteomyelitis with a slow and torpid evolution that does not tend to be healing [3]. It is a severe adverse reaction experienced by some people to certain drugs commonly used in the treatment of cancer and osteoporosis [4]. It is a potentially painful and debilitating condition that can significantly affect patients' quality of life [5]. Consultation with the dentist before starting antiresorptive or antiangiogenic pharmacological treatment considerably reduces the risk of developing MRONJ in case of interventions that cause osteonecrosis such as dental extractions [6]. Periodontal or periapical disease is associated with the occurrence of osteonecrosis and is considered a local risk factor for the disease [7].

There is a concern regarding osteonecrosis of the jaw, therefore, this literature review will help us to know the most relevant characteristics that exist and their impact in the dental area. This review article aims to analyze the literature on osteonecrosis of the jaw and the existing relationship with medications, specifically its etiology, epidemiology, oral manifestations, diagnostic methods, and treatment.

2. Materials and Methods

Articles on the subjects published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using PRISMA guidelines, i.e., identification, review, choice, and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews (AMSTAR-2) [8].

The search was performed using Boolean logical operators AND, OR and NOT.

It was realized with the words “osteonecrosis jaw”, “etiology”, “epidemiology”, “diagnostic methods”, “oral manifestations”, “treatment”, in conjunction with logical Boolean operators OR y AND.

3. Results & Discussion

3.1 Etiology

Bone is a specialized connective tissue that provides structural support and a microenvironment that facilitates various physiologic functions [9].

The first case of drug-related osteonecrosis of the jaw was reported by Marx in the early 2000s in a study of exposed nonhealing bone in the maxillofacial region of a patient treated with a bisphosphonate, an antiresorptive drug that affects the dissolution of the mineral content of bone [10].

Bisphosphonate-related osteonecrosis of the jaw is defined by the American Society for Bone and Mineral Research (ASBMR) as an area of necrotic bone [11] exposed in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and has not received radiation therapy to the craniofacial region [12, 13]. Bisphosphonates are antiresorptive, osteoclastic bone resorption blocking drugs that inhibit mineral dissolution [7, 14, 15, 16]. It is characterized by refractory bone exposure [17]. It has emerged as a severe condition in patients undergoing long-term treatment with high-dose bisphosphonates or denosumab [17, 18, 19], mainly after tooth extraction [20]. It usually appears between 4 months and 6 years after the initiation of treatment with such a drug [21]. It is a complication that has an impact on the quality of life of geriatric patients [22]. It was first described as a consequence of ionizing radiation used in the treatment of malignant tumors [23].

Although the pathogenesis of drug-related osteonecrosis of the jaw is still unclear, genetic factors have shown an important role in this disease; considering that bisphosphonates are the main ethiology of the condition.

3.2 Epidemiology

Drug-related osteonecrosis of the jaw has been found to be more prevalent in patients with high cumulative doses of bisphosphonates or other agents than in those with lower doses [24]. Dentoalveolar surgery is a major local risk factor associated with the incidence of ONJ, with 52-61% of patients reporting tooth extraction [7].

The incidence of osteonecrosis of the jaw in patients with osteoporosis is 1.04-69/100,000 patients per year treated with orally administered bisphosphonates [25, 26] and 0-90/100,000 patients per year treated intravenously [24, 26]. The actual incidence of osteonecrosis of the jaw differs according to the type of treatment being between 0.8-12% in intravenous oncological treatments, while with oral treatments for osteoporosis it is 0.01-0.04% [27, 28]. It occurs most frequently in the mandible with 65%, as in the maxilla it occurs in 28.4% and only 5.5% in both together [12, 27].

In oncologic patients with bone metastases or malignant hypercalcemia the incidence is significantly higher, up to 1-15% [29, 30].

Osteonecrosis of the jaw is more frequent in patients who ingest bisphosphonates, regardless of whether orally or intravenously, as both affect on average equally such patients, with a frequency of 65% in the jaw.

3.3 Oral Manifestations

It is important for clinicians to be aware of drug-related osteonecrosis of the jaw and the key signs and symptoms [17]; the onset is usually with pain, suppuration or else manifesting as a lack of healing in the alveolar process, with the vision of necrotic bone, but in some cases, the patient before this exposure occurs, presents with suppuration from some oral fistula, accompanied or not by pain [28], as well as swelling, cellulitis and pus exudation; hypoesthesia or paresthesia in the lower lip region (Vincent's symptom) including that of the chin, halitosis [17, 26]; and loosening of teeth [17].

A defining feature of drug-related osteonecrosis of the jaw is the exposure of clinically evident necrotic bone, which is exposed through the oral mucosa or facial skin that can lead to severe chronic pain and facial soft tissue infections [31, 32] or fistulation that can be probed into the bone surface that does not heal for more than 8 weeks. This clinical finding can be anticipated by mild pain and discomfort at the affected site [33].

There are 4 stages in order to classify bisphosphonate-induced osteonecrosis, according to the standards established by the American Association of Oral and Maxillofacial Surgeons (AAOMS) [26, 34, 35].

There are 4 stages in order to classify bisphosphonate-induced osteonecrosis

Stage 0: Patient at risk. No clinical evidence of bone necrosis is found. Presents symptoms, signs and nonspecific radiographic findings can be observed [34].
Stage I: Necrotic bone exposure is observed, asymptomatic patient with no signs of acute infection [34].
Stage II: Necrotic bone exposure is observed, with pain and signs of acute infection [34].
Stage III: Necrotic bone exposure is observed with pain, signs of acute infection, as well as cutaneous fistula and clinical and/or radiographic evidence of bone sequestration or other complication (fractures, etc.) [34].

The form in which it manifests most frequently (69%) is in the lack of healing after exodontia or else bone exposure with inflammation and infection associated with oral surgery [27, 36]. It also presents as a variable painful ulceration, usually affecting the posterior lingual mandible at the level of the mylohyoid ridge. The ulcer may persist for periods ranging from a few days to several months. Bone inflammation and infection are usually present in patients with advanced

osteonecrosis and appear to be secondary events [12]. For the localization of osteonecrosis in the jaws, an explanation was given in 2003 that it was due to the presence of teeth where there are teeth exposed to the external environment, with frequent periodontal inflammation, dental abscesses, endodontic treatments and other pathologies that increase the rate of bone turnover in the jaws [3].

Necrotic bone exposure is one of the most frequent oral manifestations in patients consuming bisphosphonates, as it occurs in stage 1, 2 and 3 of the standards established by the American Association of Oral and Maxillofacial Surgeons (AAOMS).

3.4 Diagnostic Methods

For its diagnosis it has to meet three parameters: previous treatment with antiangiogenic or antiresorptive drugs, bone exposure for more than eight weeks and absence of radiotherapy [37], which can be performed by any dentist or physician with basic knowledge [33].

Patient history and clinical oral examination [12, 36, 38] remain the most sensitive diagnostic tools for osteonecrosis [12].

Several imaging modalities are available to clarify the diagnosis and assist with staging. These include magnetic resonance imaging, computed tomography, plain radiographs, bone scintigraphy, and positron emission tomography [39].

The first diagnostic option [40] is orthopantomography, to provide an initial estimate of the extent of the disease [28, 38, 41], as radiolucent (osteolysis) and radiopaque (osteoclerosis) areas may be noted [3, 40].

Magnetic resonance imaging [38] and cone beam computed tomography or computed tomography, are used for surgical

intervention [17].

Occlusal radiographs show localized radiopacity, representing necrotic bone, superficial to the lingual cortex [3, 12]. A CT scan allows to assess the extent of the lesion and detect changes in the bone trabeculation [3, 28, 40], also confirming the clinical stage and, therefore, guiding towards the specific treatment for each case [42].

Histopathological examination [12, 28] of the necrotic bone base shows patchy areas of resorption, microbial colonization and often adherent fragments of granulation tissue with acute inflammation [12], but does not allow a conclusive diagnosis, emphasizing the need for a detailed clinical report [43].

A biopsy is only indicated to rule out bone metastases or primary bone tumors in maxilla or mandible [40].

The most characteristic diagnostic methods of osteonecrosis of the jaw include orthopantomography, magnetic resonance imaging, computed tomography, among others that clarify the diagnosis of the disease; in contrast, histopathological examination does not allow us a conclusive diagnosis.

3.5 Treatment

Treatment of osteonecrosis of the jaw is based on the stage of disease, lesion size [34] and the presence of contributing pharmacotherapy and comorbidity [12].

Treatment of osteonecrosis of the jaw [22, 35, 40].

Stage 0	There is no indicated treatment. Oral health education and instruction. Any existing dental inflammatory causes should be eliminated.
Stage 1	Use of mouth rinse, e.g. 0.12% Chlorhexidine for 3 times a day. Oral health education, instruction and motivation.
Stage 2	Antibiotic treatment. Oral health education and instruction. Debridement is not recommended due to risk of bone exposure.
State 3	Antibiotic treatment. Oral health education and instruction. Debridement is not recommended due to risk of bone exposure. Perform bone recession in very extreme cases.

Treatment strategies range from conservative local wound care to aggressive receptive surgery of all necrotic bone. Conservative strategies include systemic antibiotics, oral antibacterial rinsing, and debridement of loose necrotic bone that no longer has soft tissue coverage [11, 12].

Treatment by bone resection combined with the use of growth factors has yielded promising results in the search for a successful cure for this complication [44].

Alternative treatments such as platelet-rich plasma, low level laser irradiation, bone morphogenic protein and human parathyroid hormone (hPTH) have been suggested to eliminate pain, control soft and hard tissue infection and minimize the progression or occurrence of bone necrosis [20].

Complementary treatments to mandibular osteonecrosis are laser, growth factors, hyperbaric oxygen and ozone [45].

We can conclude that one of the treatments to consider in osteonecrosis of the jaw is education and instruction in oral hygiene that the patient should take, as well as the use of oral antibacterial rinses.

4. Conclusions

Although the pathogenesis of drug-related osteonecrosis of the jaw is still not clear, every patient treated with bisphosphonates is susceptible to present it when undergoing invasive dental procedures, affecting 65% of the jaw, therefore, the exposure of necrotic bone is one of the most frequent oral manifestations, and the most characteristic diagnostic methods to confirm it are orthopantomography,

magnetic resonance imaging, computed tomography, treatments are varied depending on the situation in which each case is, but education and instruction in oral hygiene are of utmost importance.

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